(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 November 2002 (21.11.2002)

PCT

(10) International Publication Number
WO 02/092032 A1

(51) International Patent Classification[7]: A61K 7/06

(21) International Application Number: PCT/KR02/00879

(22) International Filing Date: 11 May 2002 (11.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2001/25682 11 May 2001 (11.05.2001) KR

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/092032 A1

(54) Title: USE OF 3-POSITION CYCLOSPORIN DERIVATIVES FOR HAIR GROWTH

(57) Abstract: The present invention discloses a hair growth promoting agent comprising a cyclosporin derivative as an active ingredient, and more particularly, a hair growth promoting agent comprising a cyclosporin A derivative substituted in the 3-position as an active ingredient.

USE OF 3-POSITION CYCLOSPORIN DERIVATIVES FOR HAIR GROWTH

Technical Field

The present invention relates to a hair growth promoting agent comprising a cyclosporin derivative as an active ingredient and more particularly, to a hair growth promoting agent comprising cyclosporin derivatives modified in the 3-position as an active ingredient.

Background Art

On average, the human scalp contains about 100,000 to 150,000 hairs. Each hair has three main stages of growth: anagen, catagen and telogen, after which the hair falls out. This hair growth cycle is repetitive and the duration of one cycle is different from other cycles, ranging approximately 3 to 6 years. Thus, the average adult normally loses about 50 to 100 hairs every day. In general, alopecia refers to a phenomenon wherein duration of the anagen growth phase is shortened and the percentage of hairs in the catagen and telogen phases increases, whereby the number of lost hairs is increased excessively and abnormally.

There are many theories to explain for loss of hair, including for example, poor blood circulation, excessive functioning of male sex hormone, excessive production and secretion of sebum, deterioration of scalp by peroxides, bacteria, etc., hereditary factors, aging, stress, etc. However, explicit mechanisms have not been revealed. Recently, the population suffering from hair loss is tending to increase, since changing dietary habits and stress imposed on individuals due to modern social environments, etc. has increased. Also, the age of the individuals affected by alopecia is dropping and furthermore, the population of female alopecia sufferers is rising.

One of preparations which are most commonly used for treatment and prevention of alopecia is one that contains minoxidil. There are two hair-regrowth agents which have received approval from the U.S. Food and Drug Administration, and minoxidil is one of those approved hair-regrowth agents. Minoxidil was originally developed as a hypertension drug for the purpose of reducing blood pressure. However, when using this drug, as a side effect, a trichogenous effect

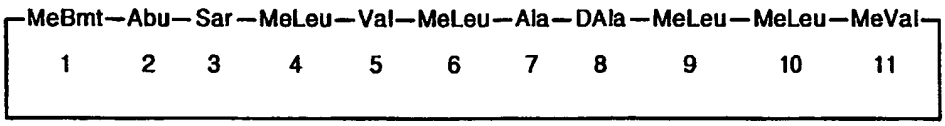
was observed and thereafter, this drug became famous as a hair-regrowth agent. Although mechanisms by which minoxidil works as a hair-regrowth agent is not clearly understood, it is inferred that minoxidil increases blood flow by expansion of blood vessels, whereby roots of hairs are supplied with more nutrition and eventually, growth of hairs are promoted.

Such a model of blood flow increase has been indirectly supported by a recent report that minoxidil enhances the expression of vascular endothelial growth factor (VEGF), a growth factor associated with vasodilatation in the dermal papilla which is a main cell making up the hair roots. Also, other than the vasodilative effect of the minoxidil in the hair-restoring mechanism, it has been reported that minoxidil promotes activation of dermal papilla cells in the roots of hair incubated *in vitro*, and growth of hair follicles in a tissue culture of follicles *in vitro*. These facts indicate that minoxidil may work directly on the roots of hair as a growth factor.

In addition, finasteride, a main component of Propecia which has started to be sold by Merck, is used for treatment of alopecia. It inhibits conversion of the male hormone testosterone into dihydrotestosterone, which is a more potent male hormone than testosterone. On December of 1997, the 1 mg finasteride tablet was approved by the US FDA as a hair-regrowth agent for treatment of male pattern hair loss in men only, and is now commercially available. In clinical studies, it has been demonstrated to have a significant trichogenous effect. However, there has been a report that finasteride may inhibit male sexual function as a side effect. Since neither finasteride nor minoxidil show superior effect in clinical tests, and there is concern about side effects, many researches are conducted to develop a new and improved hair-regrowth agents.

The cyclosporin family of drugs has immunosuppressive activity. It is also effective to inhibit growth of virus, fungus, protozoan, etc. and has various physiological effects such as nephrotoxicity, hepatotoxicity, hypertension, enlargement of periodontium, trichogenous effect, and so on, as side effects. Cyclosporin A, a representative cyclosporin, is a cyclic peptide having the following Chemical Formula, which comprises 11 amino acids, including several N-methyl amino acids and D-alanine at No. 8 residue.

[Structure Formula 1]



where MeBmt is N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine, Abu is L-α-aminobutyric acid, Sar is sarco- sine, MeLeu is N-methyl-L-leucine,Val is L-valine, Ala is L-alanine, DAla is D-alanine, MeVal is N-methyl-L-valine.

The amino acid form of cyclosporin A of the above Chemical Formula 1 is L-configuration, unless otherwise specified. The residue numbering of amino acids starts from MeBmt and proceeds clockwise, i.e. 1 for MeBmt and 11 for the last MeVal (N-methyl-L-valine) as shown in the Structure Formula 1. Nomenclature of various derivatives including cyclosporins A to Z, follows methods commonly used (Helv. Chim. Acta, 1987, 70:13-36). For example, if Abu in the 2-position of cyclosporin A is substituted with L-alanine, L-threonine, L-valine or L-norvaline, the derivatives thus prepared are named cyclosporin B, cyclosporin C, cyclosporin D or cyclosporin G, respectively. Further, when the amino acid residues of the cyclosporin derivatives differ from those of cyclosporin A, the derivatives are named by describing the substituent. For example, if sarcosine, being the amino acid residue 3 of cyclosporin A, is substituted with N-methyl-D-Abu^3 or N-methyl-D-Nva^3, the derivatives thus prepared are named [N-methyl-D-Abu^3] cyclosporin A or [N-methyl-D-Nva^3] cyclosporin A, respectively. Meanwhile, a common method for abbreviating amino acids is employed, that is, N-methyl-L-leucine is abbreviated by MeLeu, N-methyl-L-isoleucine by MeIle, N-methyl-L-Valine by MeVal, N-methyl-L-alanine by MeAla, N-methyl-L-norvaline by MeNva, L-leucine by Leu, L-isoleucine by Ile, sarcosine by Sar, L-serine by Ser, L-valine, Val, L-alanine by Ala, D-alanine by DAla, L-aminobutyric acid by Abu, L-threonine by Thr, and L-norvaline by Nva. Further, as for a derivative of cyclosporin which is substituted with sulfur instead of a carbonyl oxygen at the amino acid residue 7, the name of the derivative may be cyclosporin 7-thioamide or [$^7\psi^8$ CS-NH] cyclosporin, according to different references (Helv. Chim. Acta. 74: 1953-1990, 1991; J. Org. Chem. 58: 673-677, 1993; J. Org. Chem. 59: 7249-7258, 1994).

So far, possible development of cyclosporin as a hair-regrowth agent has been studied by many research groups. Particularly, researches involving animal hair regrowth tests, human alopecia areata (J. Am. Acad. Dermatol., 1990, 22:242-250), human male pattern alopecia (J. Am. Acad. Dermatol., 1990, 22:251-253 and Skin Pharmacol., 1994, 7:101-104), and inhibition effect of hair loss by chemotherapy in animal models (Am. J. Pathol., 1997, 150:1433-1441) have been widely conducted. In comparative experiments on mouse's back, it is shown that cyclosporin has a hair regrowth effect about 100 times superior to minoxidil Based on such

findings, there have been attempts to utilize cyclosporin as a treatment for male pattern alopecia, and many applications for patents have been filed.

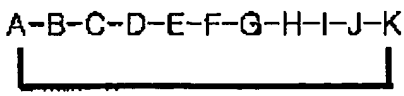
For example, Japanese Patent Publication Kokai Nos. Sho 60-243008, Sho 62-19512 and Sho 62-19513 disclose use of cyclosporin derivatives as a hair regrowth agent. Also, Europe Patent Publication No. 0414632B1 teaches a cyclosporin derivative modified in the 8-position, and PCT Publication No. 93/17039 teaches isocyclosporin. Moreover, United States Patent No. 5,807,820 and British Patent No. 2,218,334A disclose cyclosporins with excellent transdermal absorption, pursuant to the use of cyclosporins as hair restorers.

Disclosure of the Invention

Therefore, the present invention has been made in view of the above problems associated with side effects of cyclosporin A, and it is an object of the present invention to provide a hair growth promoting agent comprising a cyclosporin derivative as an active ingredient, which exerts an excellent hair growth-promotion ability.

In accordance with one aspect of the present invention, the above and other objects can be accomplished by the provision of a hair growth promoting agent comprising a 3-position analog of cyclosporin represented by the below Formula 1, as an active ingredient, which is prepared by synthesizing a variety of derivatives thereof and evaluating their hair growth promoting effects, with an aim of developing a novel agent for promoting hair growth.

[Formula 1]



wherein:

A represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine, (2S,3R,4R,6E)-3-sulfhydryl-4-methyl-2-(methylamino)-6-octenoic acid or (2S,4R,6E)-3-oxo-4-methyl-2-(methylamino)-6-octenoic acid;

B represents L-aminobutyric acid (Abu), L-alanine (Ala), L-threonine (Thr), L-valine (Val) or L-norvaline (Nva);

C represents a D-amino acid represented by the general formula 1,

[General formula 1]

CH_3NH-CH(R)-COOH

in which,

R is one selected from the group consisting of hydrogen, C_1-C_6 straight or branched

alkyl, alkenyl or alkynyl moieties, substituted or unsubstituted with one or more selected from the group consisting of amino, hydroxy, halo, haloalkyl, ester, alkoxy, cyano, nitro, alkylamino, and dialkylamino, and -X- R' represented by the general formula 2 below,

[General formula 2]

-X- R'

in which,

X is oxygen or sulfur, and

R' is one selected from the group consisting of hydrogen, and C_1-C_6 straight or branched alkyl, alkenyl or alkynyl moieties, substituted or unsubstituted with one or more selected from the group consisting of amino, hydroxy, halo, haloalkyl, ester, alkoxy, cyano, nitro, alkylamino, and dialkylamino;

D represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-valine;

E represents L-valine or L-norvaline;

F represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-leucine;

G represents L-alanine or L-alanine thioamide ([$^7\psi^8$ CS-NH], NH-CHCH$_3$-CS-);

H represents a D-amino acid represented by the general formula 3,

[General formula 3]

-NH-CH(CH_2R)-COOH

in which,

R' is hydrogen or X-R represented by the general formula 4,

[General formula 4]

-X- R'

in which,

X is oxygen or sulfur, and

R' is one selected from the group consisting of hydrogen, and C_1-C_6 straight or branched alkyl, alkenyl or alkynyl moieties, substituted or unsubstituted with one or more selected from the group consisting of amino, hydroxy, halo, haloalkyl, ester, alkoxy, cyano, nitro, alkylamino, and dialkylamino;

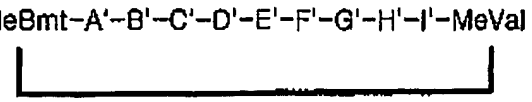
I represents N-methyl-L-leucine, γ-hydroxy-N-methyl-L-leucine or L-leucine;

J represents N-methyl-L-leucine, γ-hydroxy-N-methyl-L-leucine or L-leucine; and,

K represents N-methyl-L-valine or L-valine.

In accordance with another aspect of the invention, there is provided a hair growth promoting agent comprising a 3-position analog of cyclosporin with an excellent hair growth promoting effect, represented by Formula 2 below, as an active ingredient.

[Formula 2]



wherein:

MeBmt represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine;

A' represents L-aminobutyric acid, L-alanine, L-threonine, L-valine or L-norvaline;

B' represents N-methyl-D-aminobutyric acid, N-methyl-D-norvaline, D-2-(methylamino)hexa-4-ynoyl, D-2-(methylamino)pent-4-ynoyl, D-2-methylthio-sarcosine, N-methyl-O-propenyl-D-serine or N-methyl-D-serine;

C' represents N-methyl-L-leucine, γ-hydroxy-N-methyl-L-leucine or L-valine;

D' represents L-valine or L-norvaline;

E' represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-leucine;

F' represents L-alanine or L-alanine thioamide ([$^{7}\psi^{8}$ CS-NH], NH-$CHCH_3$-CS-);

G' represents D-alanine or D-serine;

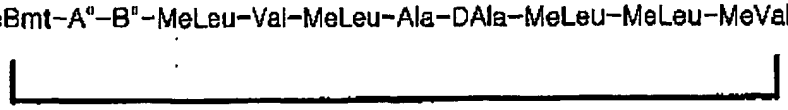
H' represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-leucine;

I' represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-leucine; and,

MeVal represents N-methyl-L-valine.

In accordance with another aspect of the invention, there is provided a hair growth promoting agent comprising a 3-position analog of cyclosporin with an excellent hair growth promoting effect, represented by Formula 3 below, as an active ingredient,

[Formula 3]



wherein:

MeBmt represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine;

A" represents L-alanine, L-threonine, L-valine or L-norvaline;

B" represents N-methyl-D-aminobutyric acid, N-methyl-D-norvaline, D-2-(methylamino)hexa-4-ynoyl, D-2-(methylamino)pent-4-ynoyl, D-2-methylthio-sarcosine, N-methyl-O-propenyl-D-serine or N-methyl-D-serine;

MeLeu represents N-methyl-L-leucine;

Val represents L-valine;
Ala represents L-alanine;
DAla represents D-alanine; and,
MeVal represents N-methyl-L-valine.

In accordance with yet another aspect of the present invention, there is provided a hair growth promoting agent, whose composition comprising a 3-position analog of cyclosporin may be formulated in the form of liquid formualtions, sprays, gels, pastes, emulsions, creams, conditioners or shampoos.

Brief Description of the Drawings

The above and other objects, features and other advantages of the present invention will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawing, in which:

Fig. 1 is a ^{1}H-NMR spectrum of [N-methyl-D-Abu^{3}] cyclosporin A;
Fig. 2 is a ^{13}C-NMR spectrum of [N-methyl-D-Abu^{3}] cyclosporin A;
Fig. 3 is a ^{1}H-NMR spectrum of [N-methyl-D-Nva^{3}] cyclosporin A;
Fig. 4 is a ^{13}C-NMR spectrum of [N-methyl-D-Nva^{3}] cyclosporin A;
Fig. 5 is a ^{1}H-NMR spectrum of [D-2-(methylamino)hexa-4-ynoyl^{3}] cyclosporin A;
Fig. 6 is a ^{13}C-NMR spectrum of [D-2-(methylamino)hexa-4-ynoyl^{3}] cyclosporin A;
Fig. 7 is a ^{1}H-NMR spectrum of [D-2-(methylamino)pent-4-ynoyl^{3}] cyclosporin A;
Fig. 8 is a ^{13}C-NMR spectrum of [D-2-(methylamino)pent-4-ynoyl^{3}] cyclosporin A;
Fig. 9 is a ^{1}H-NMR spectrum of [D-2-(methylthio)-Sar^{3}] cyclosporin A;
Fig. 10 is a ^{13}C-NMR spectrum of [D-2-(methylthio)-Sar^{3}] cyclosporin A;
Fig. 11 is a ^{1}H-NMR spectrum of [N-methyl-O-propenyl-D-Ser^{3}] cyclosporin A;
Fig. 12 is a ^{13}C-NMR spectrum of [N-methyl-O-propenyl-D-Ser^{3}] cyclosporin A;
Fig. 13 is a ^{1}H-NMR spectrum of [N-methyl-D-Ser^{3}] cyclosporin A; and
Fig. 14 is a ^{13}C-NMR spectrum of [N-methyl-D-Ser^{3}] cyclosporin A.

Best Mode for Carrying Out the Invention

Hereinafter, the present invention will be described in detail, in conjunction with various examples. These examples are provided only for illustrative purposes, and the present invention is not to be construed as being limited to those examples.

With the aim of developing a novel agent with hair growth promoting effect, the present inventors chemically synthesized a variety of 3-position analogs of cyclosporin, and hair growth promoting effects thereof were examined. Thus, the invention provides a hair growth promoting agent comprising a cyclosporin derivative as an active ingredient,

Example 1: Synthesis of 3-position analog of cyclosporin

A general method for the alkylation of cyclosporin A was as follows. Tetrahydrofuran (THF) was added with diisopropyl amine ($(i\text{-}Pr)_2NH$) and added with a solution of n-butyl lithium (BuLi) in hexane under nitrogen atmosphere at -78°C, followed by stirring for 30 min. To the solution of LDA (lithium diisopropylamide) thus prepared, cyclosporin A in THF was added, stirred for 1 hr, and electrophile was added.

1-1: Synthesis of [N-methyl-D-Abu^3] cyclosporin A: Compound 1

According to the general method above, to a solution of 10 equivalents of LDA was added 1.0 g cyclosporin A in 50 ml THF at -78 °C. The reaction mixture was stirred for 2 hrs at -78 °C and added with 0.4 ml ethyliodide. After the temperature of the solution reached room temperature, the solution was further stirred for 24 hrs and added with 20 ml water, followed by concentration. The residue was added with ether (Et_2O), washed with water and a solution of saturated sodium chloride in sequence, and dried over anhydrous $MgSO_4$. After concentrating, the residue was subjected to silica gel column chromatography (100 g silica gel, dichloromethane : methylalcohol = 96 : 4), followed by HPLC to give 0.1 g of the title compound.

Molecular weight of the compound was determined by FAB MS (ZMS AX 505H) analysis. To confirm the molecular structure, Nuclear Magnetic Resonance (NMR) measurements were performed on 600 MHz (Bruker) for ^{1}H-NMR and on 150 MHz (Bruker) for ^{13}C-NMR, and the spectra are shown in Figs. 1 and 2, respectively.

1-2: Synthesis of [N-methyl-D-Nva^3] cyclosporin A: Compound 2

According to the general method, to a solution of 10 equivalents of LDA was added 1.0 g cyclosporin A in 50 ml THF at -78 °C. The reaction mixture was stirred for 2 hrs at -78 °C and added with 0.41 ml propyliodide. After the temperature of the solution reached room temperature, the solution was further stirred for 24 hrs and added with 20 ml water, followed by concentration. The residue was added with ether (Et_2O), washed with water and a solution of saturated sodium chloride in sequence, and dried over anhydrous $MgSO_4$. After

concentrating, the residue was subjected to silica gel column chromatography (100 g silica gel, dichloromethane : methylalcohol = 96 : 4), followed by HPLC to give 0.12 g of the title compound. Molecular weight of the compound was determined by FAB MS (ZMS AX 505H) analysis. To confirm the molecular structure, Nuclear Magnetic Resonance (NMR) measurements were performed on 600 MHz (Bruker) for ^{1}H-NMR and on 150 MHz (Bruker) for ^{13}C-NMR, and the spectra are shown in Figs. 3 and 4, respectively.

1-3: Synthesis [D-2-(methylamino)hexa-4-ynoyl^{3}] cyclosporin A: Compound 3

According to the general method, to a solution of 10 equivalents of LDA was added 1.0 g cyclosporin A in 50 ml THF at -78 °C. The reaction mixture was stirred for 2 hrs at -78 °C and added with 0.73 ml 1-bromo-2-butyne. After the temperature of the solution reached room temperature, the solution was further stirred for 24 hrs and added with 20 ml water, followed by concentration. The residue was added with ether (Et_2O), washed with water and a solution of saturated sodium chloride in sequence, and dried over anhydrous $MgSO_4$. After concentrating, the residue was subjected to silica gel column chromatography (100 g silica gel, dichloromethane : methylalcohol = 96 : 4), followed by HPLC to give 0.13 g of the title compound. Molecular weight of the compound was determined by FAB MS (ZMS AX 505H) analysis. To confirm the molecular structure, Nuclear Magnetic Resonance (NMR) measurements were performed on 600 MHz (Bruker) for ^{1}H-NMR and on 150 MHz (Bruker) for ^{13}C-NMR, and the spectra are shown in Figs. 5 and 6, respectively.

1-4: Synthesis of [D-2-(methylamino)pent-4-ynoyl^{3}] cyclosporin A: Compound 4

According to the general method, alkylation was performed employing THF (200 ml), $(i\text{-}Pr)_2NH$ (3.2 ml), BuLi (8 ml), cyclosporin A (3.76 g) in 50 ml THF and propargyl bromide (3.57 g). After the temperature of the solution reached room temperature, the solution was further stirred for 24 hrs and added with 40 ml water, followed by concentration. The residue was added with ether (Et_2O), washed with water and a solution of saturated sodium chloride in sequence, and dried over anhydrous $MgSO_4$. After concentrating, the residue was subjected to silica gel column chromatography (100 g silica gel, dichloromethane : methylalcohol = 96 : 4), followed by HPLC to give the title compounds 3 (0.18 g) and 4 (0.08 g). Molecular weight of the compound was determined by FAB MS (ZMS AX 505H) analysis. To confirm the molecular structure, Nuclear Magnetic Resonance (NMR) measurements were performed on 600 MHz (Bruker) for ^{1}H-NMR and on 150 MHz (Bruker) for ^{13}C-NMR, and the spectra are shown in Figs. 7 and 8, respectively.

1-5: Synthesis of [D-2-(methylthio)-Sar^3] cyclosporin A: Compound 5

According to the general method, alkylation was performed employing THF (100 ml), $(i\text{-}Pr)_2NH$ (1.6 ml), BuLi (4.0 ml), cyclosporin A (1.0 g) in 30 ml THF and methyl disulfide (Me_2S_2) (1.5 ml). The solution was stirred for 14 hrs at 0 °C and added with 20 ml water, followed by concentration. The residue was added with ether (Et_2O), washed with water and a solution of saturated sodium chloride in sequence, and dried over anhydrous $MgSO_4$. After concentrating, the residue was subjected to silica gel column chromatography (100 g silica gel, dichloromethane : methylalcohol = 50 : 1 ~ 96 : 4), followed by HPLC to give the title compounds 5 (0.36 g) and 6 (0.05 g). Molecular weight of the compound was determined by FAB MS (ZMS AX 505H) analysis. To confirm the molecular structure, Nuclear Magnetic Resonance (NMR) measurements were performed on 600 MHz (Bruker) for ^{1}H-NMR and on 150 MHz (Bruker) for ^{13}C-NMR, and the spectra are shown in Figs. 9 and 10, respectively.

1-6: Synthesis of [N-methyl-O-propenyl-D-Ser^3] cyclosporin A: Compound 6

According to the general method, [D-methylserine^3] cyclosporin A (0.62 g, 0.5 mmol), tetrabutylammonium chloride (0.11 g, 0.5 mmol), and aryl bromide (0.24 g, 2.0 mmol) were dissolved in dichloromethane (50 ml), then added with 30 % NaOH (1.5 ml), and the mixture was stirred for 2 hrs. After adding with 50 ml dichloromethane, the solution was washed with water and a solution of saturated sodium chloride in sequence, and dried over anhydrous $MgSO_4$. The concentrated residue was subjected to silica gel column chromatography (100 g silica gel, dichloromethane : methylalcohol = 97 : 3), followed by HPLC to give 0.4 g of the title compound. Molecular weight of the compound was determined by FAB MS (ZMS AX 505H) analysis. To confirm the molecular structure, Nuclear Magnetic Resonance (NMR) measurements were performed on 600 MHz (Bruker) for ^{1}H-NMR and on 150 MHz (Bruker) for ^{13}C-NMR, and the spectra are shown in Figs. 11 and 12, respectively.

1-7: Synthesis of [N-methyl-D-Ser^3] cyclosporin A: Compound 7

According to the general method, to a solution of 10 equivalents of LDA was added 1.0 g cyclosporin A in 50 ml THF at -78 °C. The reaction mixture was stirred for 2 hrs at -78 °C and added with 2.0 g paraformaldehyde. After the temperature of the solution reached room temperature, the solution was further stirred for 24 hrs and added with 20 ml water, followed by concentration. The residue was added with ether (Et_2O), washed with water and a solution of saturated sodium chloride in sequence, and dried over anhydrous $MgSO_4$. After

concentrating, the residue was subjected to silica gel column chromatography (100 g silica gel, dichloromethane : methylalcohol = 96 : 4), followed by HPLC to give 0.3 g of the title compound. Molecular weight of the compound was determined by FAB MS (ZMS AX 505H) analysis. To confirm the molecular structure, Nuclear Magnetic Resonance (NMR) measurements were performed on 600 MHz (Bruker) for ^{1}H-NMR and on 150 MHz (Bruker) for ^{13}C-NMR, and the spectra are shown in Figs. 13 and 14, respectively.

Preparative example 1: hair tonic

1-1: Preparation of hair tonic containing [N-methyl-D-Abu^{3}] cyclosporin A

Individual ingredients were mixed and stirred, and the mixtures were completely dissolved to prepare three hair growth promoting tonics, with compositions as shown in Table 1 below. It was found that the composition 1 of Table 1 has a hair growth promoting effect at a level similar to a conventional hair tonic containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 1: Formulation of hair tonic

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
ethanol	40.0	40.0	40.0
[N-methyl-D-Abu^{3}] cyclosporin A	0.1	1.0	8.0
tocopherol acetate	0.1	0.1	0.1
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Tween 20	0.5	0.5	0.5
flavor	typical	typical	typical
colarant	typical	typical	typical
water	balance	balance	balance

1-2: Preparation of hair tonic containing [N-methyl-D-Nva^{3}] cyclosporin A

Individual ingredients were mixed and stirred, and the mixtures were completely dissolved to prepare three hair growth promoting tonics, with compositions as shown in Table 2 below. It was found that the composition 1 of Table 2 has a hair growth promoting effect at a level similar to a conventional hair tonic containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 2: Formulation of hair tonic

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
ethanol	40.0	40.0	40.0
[N-methyl-D-Nva^3] cyclosporin A	0.1	1.0	8.0
tocopherol acetate	0.1	0.1	0.1
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Tween 20	0.5	0.5	0.5
flavor	typical	typical	typical
colarant	typical	typical	typical
water	balance	balance	balance

1-3: Preparation of hair tonic containing [D-2-(methylamino)hexa-4-ynoyl^3] cyclosporin A

Individual ingredients were mixed and stirred, and the mixtures were completely dissolved to prepare three hair growth promoting tonics, with compositions as shown in Table 3 below. It was found that the composition 1 of Table 3 has a hair growth promoting effect at a level similar to a conventional hair tonic containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 3: Formulation of hair tonic

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
ethanol	40.0	40.0	40.0
[D-2-(methylamino)hexa-4-ynoyl ^{3}] cyclosporin A	0.1	1.0	8.0
tocopherol acetate	0.1	0.1	0.1
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Tween 20	0.5	0.5	0.5
flavor	typical	typical	typical
colarant	typical	typical	typical
water	balance	balance	balance

1-4: Preparation of hair tonic containing [D-2-(methylamino)pent-4-ynoyl^3]

cyclosporin A

Individual ingredients were mixed and stirred, and the mixtures were completely dissolved to prepare three hair growth promoting tonics, with compositions as shown in Table 4 below. It was found that the composition 1 of Table 4 has a hair growth promoting effect at a level similar to a conventional hair tonic containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 4: Formulation of hair tonic

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
ethanol	40.0	40.0	40.0
[D-2-(methylamino)pent-4-ynoyl^3] cyclosporin A	0.1	1.0	8.0
tocopherol acetate	0.1	0.1	0.1
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Tween 20	0.5	0.5	0.5
flavor	typical	typical	typical
colarant	typical	typical	typical
water	balance	balance	balance

1-5: Preparation of hair tonic containing [D-2-methylthio-Sar^3] cyclosporin A

Individual ingredients were mixed and stirred, and the mixtures were completely dissolved to prepare three hair growth promoting tonics, with compositions as shown in Table 5 below. It was found that the composition 1 of Table 5 has a hair growth promoting effect at a level similar to a conventional hair tonic containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 5: Formulation of hair tonic

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
ethanol	40.0	40.0	40.0
[D-2-(methylthio)-Sar^3] cyclosporin A	0.1	1.0	8.0
tocopherol acetate	0.1	0.1	0.1
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3

Tween 20	0.5	0.5	0.5
flavor	typical	typical	typical
colarant	typical	typical	typical
water	balance	balance	balance

1-6: Preparation of hair tonic containing [N-methyl-O-propenyl-D-Ser^3] cyclosporin A

Individual ingredients were mixed and stirred, and the mixtures were completely dissolved to prepare three hair growth promoting tonics, with compositions as shown in Table 6 below. It was found that the composition 1 of Table 6 has a hair growth promoting effect at a level similar to a conventional hair tonic containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 6: Formulation of hair tonic

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
ethanol	40.0	40.0	40.0
[N-methyl-O-propenyl-D-Ser^3] cyclosporin A	0.1	1.0	8.0
tocopherol acetate	0.1	0.1	0.1
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Tween 20	0.5	0.5	0.5
flavor	typical	typical	typical
colarant	typical	typical	typical
water	balance	balance	balance

1-7: Preparation of hair tonic containing [N-methyl-D-Ser^3] cyclosporin A

Individual ingredients were mixed and stirred, and the mixtures were completely dissolved to prepare three hair growth promoting tonics, with compositions as shown in Table 7 below. It was found that the composition 1 of Table 7 has a hair growth promoting effect at a level similar to a conventional hair tonic containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 7: Formulation of hair tonic

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
ethanol	40.0	40.0	40.0
[N-methyl-D-Ser^3] cyclosporin A	0.1	1.0	8.0
tocopherol acetate	0.1	0.1	0.1
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Tween 20	0.5	0.5	0.5
flavor	typical	typical	typical
colarant	typical	typical	typical
water	balance	balance	balance

Preparative example 2: hair cream

2-1: Preparation of hair cream containing [N-methyl-D-Abu^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair creams, with compositions as shown in Table 8 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

It was found that the composition 1 of Table 8 has a hair growth promoting effect at a level similar to a conventional hair cream containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 8: Formulation of hair cream

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
paraffin	5.0	5.0	5.0
cetostearyl alcohol	5.5	5.5	5.5
petrolatum	5.5	5.5	5.5
glycerin monostearate	3.0	3.0	3.0
polyoxyethyleneoctyldodecylether	3.0	3.0	3.0
propylparaben	0.3	0.3	0.3

[N-methyl-D-Abu^3] cyclosporin A	0.1	1.0	8.0
glycerin	7.0	7.0	7.0
dipropyleneglycol	20.0	20.0	20.0
polyethyleneglycol	5.0	5.0	5.0
water	balance not including flavor and colorant		
flavor	typical	typical	typical
colorant	typical	typical	typical

2-2: Preparation of hair cream containing [N-methyl-D-Nva^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair creams, with compositions as shown in Table 9 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

It was found that the composition 1 of Table 9 has a hair growth promoting effect at a level similar to a conventional hair cream containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 9: Formulation of hair cream

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
paraffin	5.0	5.0	5.0
cetostearyl alcohol	5.5	5.5	5.5
petrolatum	5.5	5.5	5.5
glycerin monostearate	3.0	3.0	3.0
polyoxyethyleneoctyldodecylether	3.0	3.0	3.0
propylparaben	0.3	0.3	0.3
[N-methyl-D-Nva^3] cyclosporin A	0.1	1.0	8.0
glycerin	7.0	7.0	7.0
dipropyleneglycol	20.0	20.0	20.0
polyethyleneglycol	5.0	5.0	5.0
water	balance not including flavor and colorant		
flavor	typical	typical	typical
colorant	typical	typical	typical

2-3: Preparation of hair cream containing [D-2-(methylamino)hexa-4-ynoyl^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair creams, with compositions as shown in Table 10 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

It was found that the composition 1 of Table 10 has a hair growth promoting effect at a level similar to a conventional hair cream containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later

Table 10: Formulation of hair cream

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
paraffin	5.0	5.0	5.0
cetostearyl alcohol	5.5	5.5	5.5
petrolatum	5.5	5.5	5.5
glycerin monostearate	3.0	3.0	3.0
polyoxyethyleneoctyldodecylether	3.0	3.0	3.0
propylparaben	0.3	0.3	0.3
[D-2-(methylamino)hexa-4-ynoyl ^{3}]cyclosporin A	0.1	1.0	8.0
glycerin	7.0	7.0	7.0
dipropyleneglycol	20.0	20.0	20.0
polyethyleneglycol	5.0	5.0	5.0
water	balance not including flavor and colorant		
flavor	typical	typical	typical
colorant	typical	typical	typical

2-4: Preparation of hair cream containing [D-2-(methylamino)pent-4-ynoyl^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair creams, with compositions as shown in

Table 11 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

It was found that the composition 1 of Table 11 has a hair growth promoting effect at a level similar to a conventional hair cream containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 11: Formulation of hair cream

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
paraffin	5.0	5.0	5.0
cetostearyl alcohol	5.5	5.5	5.5
petrolatum	5.5	5.5	5.5
glycerin monostearate	3.0	3.0	3.0
polyoxyethyleneoctyldodecylether	3.0	3.0	3.0
propylparaben	0.3	0.3	0.3
[D-2-(methylamino)pent-4-ynoyl^3] cyclosporin A	0.1	1.0	8.0
glycerin	7.0	7.0	7.0
dipropyleneglycol	20.0	20.0	20.0
polyethyleneglycol	5.0	5.0	5.0
water	balance not including flavor and colorant		
flavor	typical	typical	typical
colorant	typical	typical	typical

2-5: Preparation of hair cream containing [D-2-methylthio-Sar^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair creams, with compositions as shown in Table 12 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

It was found that the composition 1 of Table 12 has a hair growth promoting effect at a level similar to a conventional hair cream containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 12: Formulation of hair cream

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
paraffin	5.0	5.0	5.0
cetostearyl alcohol	5.5	5.5	5.5
petrolatum	5.5	5.5	5.5
glycerin monostearate	3.0	3.0	3.0
polyoxyethyleneoctyldodecylether	3.0	3.0	3.0
propylparaben	0.3	0.3	0.3
[D-2-methylthio-Sar^3] cyclosporin A	0.1	1.0	8.0
glycerin	7.0	7.0	7.0
dipropyleneglycol	20.0	20.0	20.0
polyethyleneglycol	5.0	5.0	5.0
water	balance not including flavor and colorant		
flavor	typical	typical	typical
colorant	typical	typical	typical

2-6: Preparation of hair cream containing [N-methyl-O-propenyl-D-Ser^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair creams, with compositions as shown in Table 13 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

It was found that the composition 1 of Table 13 has a hair growth promoting effect at a level similar to a conventional hair cream containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 13: Formulation of hair cream

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
paraffin	5.0	5.0	5.0
cetostearyl alcohol	5.5	5.5	5.5
petrolatum	5.5	5.5	5.5

glycerin monostearate	3.0	3.0	3.0
polyoxyethyleneoctyldodecylether	3.0	3.0	3.0
propylparaben	0.3	0.3	0.3
[N-methyl-O-propenyl-D-Ser^3] cyclosporin A	0.1	1.0	8.0
glycerin	7.0	7.0	7.0
dipropyleneglycol	20.0	20.0	20.0
polyethyleneglycol	5.0	5.0	5.0
water	balance not including flavor and colorant		
flavor	typical	typical	typical
colorant	typical	typical	typical

2-7: Preparation of hair cream containing [N-methyl-D-Ser^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair cream, with compositions as shown in Table 14 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

It was found that the composition 1 of Table 14 has a hair growth promoting effect at a level similar to a conventional hair cream containing 0.1 % cyclosporin A, as evaluated in an animal experiment according to the Test Example described later.

Table 14: Formulation of hair cream

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
paraffin	5.0	5.0	5.0
cetostearyl alcohol	5.5	5.5	5.5
petrolatum	5.5	5.5	5.5
glycerin monostearate	3.0	3.0	3.0
polyoxyethyleneoctyldodecylether	3.0	3.0	3.0
propylparaben	0.3	0.3	0.3
[N-methy-D-Ser^3] cyclosporin A	0.1	1.0	8.0
glycerin	7.0	7.0	7.0
dipropyleneglycol	20.0	20.0	20.0
polyethyleneglycol	5.0	5.0	5.0

water	balance not including flavor and colorant		
flavor	typical	typical	typical
colorant	typical	typical	typical

Preparative example 3: shampoo

3-1: Preparation of shampoo containing [N-methyl-D-Abu^3] cyclosporin A

All individual ingredients, except flavor, colorant and water, were mixed and the mixture was completely dissolved by heating, while stirring. After cooling to room temperature, the mixture was mixed with flavor and colorant. Water was finally added to adjust to 100 % the total weight, to prepare three shampoos, with compositions as shown in Table 15 below.

Table 15: Formulation of shampoo

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
sodium POE laurylsulfuric acid (30 wt% aqueous solution)	40.0	40.0	40.0
palm oil fattyacid diethanolamide	3.0	3.0	3.0
propyleneglycol	2.0	2.0	2.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
ehtanol	2.0	2.0	2.0
[N-methyl-D-Abu^3] cyclosporin A	1.0	3.0	10.0
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
flavor	typical	typical	typical
colorant	typical	typical	typical
water	balance	balance	balance

3-2: Preparation of shampoo containing [N-methyl-D-Nva^3] cyclosporin A

All individual ingredients, except flavor, colorant and water, were mixed and the mixture was completely dissolved by heating, while stirring. After cooling to room temperature, the mixture was mixed with flavor and colorant. Water was finally added to adjust to 100 % the total weight, to prepare three shampoos, with compositions as shown in Table 16 below.

Table 16: Formulation of shampoo

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
sodium POE laurylsulfuric acid (30 wt% aqueous solution)	40.0	40.0	40.0
palm oil fattyacid diethanolamide	3.0	3.0	3.0
propyleneglycol	2.0	2.0	2.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
ehtanol	2.0	2.0	2.0
[N-methyl-D-Nva^3] cyclosporin A	1.0	3.0	10.0
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
flavor	typical	typical	typical
colorant	typical	typical	typical
water	balance	balance	balance

3-3: Preparation of shampoo containing [D-2-(methylamino)hexa-4-ynoyl^3] cyclosporin A

All individual ingredients, except flavor, colorant and water, were mixed and the mixture was completely dissolved by heating, while stirring. After cooling to room temperature, the mixture was mixed with flavor and colorant. Water was finally added to adjust to 100 % the total weight, to prepare three shampoos, with compositions as shown in Table 17 below.

Table 17: Formulation of shampoo

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
sodium POE laurylsulfuric acid (30 wt% aqueous solution)	40.0	40.0	40.0
palm oil fattyacid diethanolamide	3.0	3.0	3.0
Propyleneglycol	2.0	2.0	2.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
Ethanol	2.0	2.0	2.0
[D-2-(methylamino)hexa-4-ynoyl^3] cyclosporin A	1.0	3.0	10.0
salicylic acid	0.3	0.3	0.3

L-menthol	0.3	0.3	0.3
Flavor	typical	typical	typical
Colorant	typical	typical	typical
Water	balance	balance	balance

3-4: Preparation of shampoo containing [D-2-(methylamino)pent-4-ynoyl^3] cyclosporin A

All individual ingredients, except flavor, colorant and water, were mixed and the mixture was completely dissolved by heating, while stirring. After cooling to room temperature, the mixture was mixed with flavor and colorant. Water was finally added to adjust to 100 % the total weight, to prepare three shampoos, with compositions as shown in Table 18 below.

Table 18: Formulation of shampoo

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
sodium POE laurylsulfuric acid (30 wt% aqueous solution)	40.0	40.0	40.0
palm oil fattyacid diethanolamide	3.0	3.0	3.0
propyleneglycol	2.0	2.0	2.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
ehtanol	2.0	2.0	2.0
[D-2-(methylamino)pent-4-ynoyl^3] cyclosporin A	1.0	3.0	10.0
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
flavor	typical	typical	typical
colorant	typical	typical	typical
water	balance	balance	balance

3-5: Preparation of shampoo containing [D-2-methylthio-Sar^3] cyclosporin A

All individual ingredients, except flavor, colorant and water, were mixed and the mixture was completely dissolved by heating, while stirring. After cooling to room temperature, the mixture was mixed with flavor and colorant. Water was finally added to adjust to 100 % the total weight, to prepare three shampoos, with compositions as shown in Table 19 below.

Table 19: Formulation of shampoo

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
sodium POE laurylsulfuric acid (30 wt% aqueous solution)	40.0	40.0	40.0
palm oil fattyacid diethanolamide	3.0	3.0	3.0
Propyleneglycol	2.0	2.0	2.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
Ethanol	2.0	2.0	2.0
[D-2-methylthio-Sar^3] cyclosporin A	1.0	3.0	10.0
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Flavor	typical	typical	typical
Colorant	typical	typical	typical
Water	balance	balance	balance

3-6: Preparation of shampoo containing [N-methyl-O-propenyl-D-Ser^3] cyclosporin A

All individual ingredients, except flavor, colorant and water, were mixed and the mixture was completely dissolved by heating, while stirring. After cooling to room temperature, the mixture was mixed with flavor and colorant. Water was finally added to adjust to 100 % the total weight, to prepare three shampoos, with compositions as shown in Table 20 below.

Table 20: Formulation of shampoo

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
sodium POE laurylsulfuric acid (30 wt% aqueous solution)	40.0	40.0	40.0
palm oil fattyacid diethanolamide	3.0	3.0	3.0
Propyleneglycol	2.0	2.0	2.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
Ethanol	2.0	2.0	2.0
[N-methyl-O-propenyl-D-Ser^3] cyclosporin A	1.0	3.0	10.0
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3

Flavor	typical	typical	typical
Colorant	typical	typical	typical
Water	balance	balance	balance

3-7: Preparation of shampoo containing [N-methyl-D-Ser^3] cyclosporin A

All individual ingredients, except flavor, colorant and water, were mixed and the mixture was completely dissolved by heating, while stirring. After cooling to room temperature, the mixture was mixed with flavor and colorant. Water was finally added to adjust to 100 % the total weight, to prepare three shampoos, with compositions as shown in Table 21 below.

Table 21: Formulation of shampoo

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
sodium POE laurylsulfuric acid (30 wt% aqueous solution)	40.0	40.0	40.0
palm oil fattyacid diethanolamide	3.0	3.0	3.0
propyleneglycol	2.0	2.0	2.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
ehtanol	2.0	2.0	2.0
[N-methyl-D-Ser^3] cyclosporin A	1.0	3.0	10.0
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
flavor	typical	typical	typical
colorant	typical	typical	typical
water	balance	balance	balance

Preparative example 4: hair conditioner

4-1: Preparation of hair conditioner containing [N-methyl-D-Abu^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair conditioners, with compositions as shown in Table 22 below. Water was added to adjust to 100 % the total weight including the

oil-phase and water-phase ingredients.

Table 22: Formulation of hair conditioner

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
cetanol	3.0	3.0	3.0
self-emulsifiable glycerol-monostearate	2.0	2.0	3.0
squalene	10.0	10.0	10.0
[N-methyl-D-Abu^3] cyclosporin A	1.0	5.0	10.0
propyleneglycol	2.0	2.0	2.0
stearyldimethyl benzylammonium chloride (25 wt% aqueous solution)	8.0	8.0	8.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
water	balance	balance	balance
flavor	typical	typical	typical
colorant	typical	typical	typical

4-2: Preparation of hair conditioner containing [N-methyl-D-Nva^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair conditioners, with compositions as shown in Table 23 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

Table 23: Formulation of hair conditioner

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
cetanol	3.0	3.0	3.0
self-emulsifiable glycerol-monostearate	2.0	2.0	3.0
squalene	10.0	10.0	10.0
[N-methyl-D-Nva^3] cyclosporin A	1.0	5.0	10.0
propyleneglycol	2.0	2.0	2.0

stearyldimethyl benzylammonium chloride (25 wt% aqueous solution)	8.0	8.0	8.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
water	balance	balance	balance
flavor	typical	typical	typical
colorant	typical	typical	typical

4-3: Preparation of hair conditioner containing [D-2-(methylamino)hexa-4-ynoyl^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair conditioners, with compositions as shown in Table 24 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

Table 24: Formulation of hair conditioner

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
cetanol	3.0	3.0	3.0
self-emulsifiable glycerol-monostearate	2.0	2.0	3.0
squalene	10.0	10.0	10.0
[D-2-(methylamino)hexa-4-ynoyl ^{3}] cyclosporin A	1.0	5.0	10.0
propyleneglycol	2.0	2.0	2.0
stearyldimethyl benzylammonium chloride (25 wt% aqueous solution)	8.0	8.0	8.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
water	balance	balance	balance
flavor	typical	typical	typical
colorant	typical	typical	typical

4-4: Preparation of hair conditioner containing [D-2-(methylamino)pent-4-ynoyl^3] cyclosporin

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair conditioners, with compositions as shown in Table 25 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

Table 25: Formulation of hair conditioner

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
cetanol	3.0	3.0	3.0
self-emulsifiable glycerol-monostearate	2.0	2.0	3.0
squalene	10.0	10.0	10.0
[D-2-(methylamino)pent-4-ynoyl^3] cyclosporin A	1.0	5.0	10.0
propyleneglycol	2.0	2.0	2.0
stearyldimethyl benzylammonium chloride (25 wt% aqueous solution)	8.0	8.0	8.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
water	balance	balance	balance
flavor	typical	typical	typical
colorant	typical	typical	typical

4-5: Preparation of hair conditioner containing [D-2-methylthio-Sar^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair conditioners, with compositions as shown in Table 26 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

Table 26: Formulation of hair conditioner

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
cetanol	3.0	3.0	3.0
self-emulsifiable glycerol-monostearate	2.0	2.0	3.0
squalene	10.0	10.0	10.0
[D-2-methylthio-Sar^3] cyclosporin A	1.0	5.0	10.0
propyleneglycol	2.0	2.0	2.0
stearyldimethyl benzylammonium chloride (25 wt% aqueous solution)	8.0	8.0	8.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
water	balance	balance	balance
flavor	typical	typical	typical
colorant	typical	typical	typical

4-6: Preparation of hair conditioner containing [N-methyl-O-propenyl-D-Ser^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair conditioners, with compositions as shown in Table 27 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

Table 27: Formulation of hair conditioner

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
cetanol	3.0	3.0	3.0
self-emulsifiable glycerol-monostearate	2.0	2.0	3.0
squalene	10.0	10.0	10.0
[N-methyl-O-propenyl-D-Ser^3] cyclosporin A	1.0	5.0	10.0
propyleneglycol	2.0	2.0	2.0
stearyldimethyl benzylammonium chloride	8.0	8.0	8.0

(25 wt% aqueous solution)			
methyl paraoxybenzoic acid	0.2	0.2	0.2
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
water	balance	balance	balance
flavor	typical	typical	typical
colorant	typical	typical	typical

4-7: Preparation of hair conditioner containing [N-methyl-D-Ser^3] cyclosporin A

Individual oil-phase and water-phase ingredients were mixed in a separate container, and each mixture was completely dissolved by heating to 80 °C. Two phases of the ingredients were mixed, emulsified, and cooled to room temperature. Additives such as flavor and colorant were admixed to prepare three hair conditioners, with compositions as shown in Table 28 below. Water was added to adjust to 100 % the total weight including the oil-phase and water-phase ingredients.

Table 28: Formulation of hair conditioner

(unit: weight %)

Ingredients	Comp. 1	Comp. 2	Comp. 3
cetanol	3.0	3.0	3.0
self-emulsifiable glycerol-monostearate	2.0	2.0	3.0
squalene	10.0	10.0	10.0
[N-methyl-D-Ser^3] cyclosporin A	1.0	5.0	10.0
propyleneglycol	2.0	2.0	2.0
stearyldimethyl benzylammonium chloride (25 wt% aqueous solution)	8.0	8.0	8.0
methyl paraoxybenzoic acid	0.2	0.2	0.2
salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
water	balance	balance	balance
flavor	typical	typical	typical
colorant	typical	typical	typical

Test Example: Test for hair growth promoting effect of cyclosporin derivatives of the invention

Female C57BL/6 mice of ages 6 to 7 weeks were utilized. After removing hairs on the middle of the back with an electric shaver, the mice were weighed and randomly assigned to the test groups with an even distribution of weights. The mice were given one day for adaptation. From the next day, mice were applied once a day on their backs with cyclosporin A and the cyclosporin A derivatives (Compounds 1 to 7) prepared by HPLC in Example 1 in amounts of 100 μl (conc. 0.1% w/v) for 30 days. The results were determined by visual approach, in terms of degrees of hair regrowth. With respect to respective hair-removed areas, rates of new hair growth were examined and compared.

As can be seen in Table 29, cyclosporin derivatives of the invention have a significant hair growth promoting effect, compared to the control in which mice were applied with a vehicle only. Further, the derivatives show a similar level of hair growth promoting effect, with respect to cyclosporin A. Meanwhile, over a course of 30 days, as comparing the appearance of the backs, the mice of the control and all test groups showed no specific skin irritation.

Table 29: Evaluation of cyclosporin derivatives based on hair regrowth in mice

Compound applied	vehicle	cyclosporin A	1	2	3	4	5	6	7
Area rate of hair regrowth (%)	35	91	95	91	95	96	93	94	90

On the basis of the foregoing results, the cyclosporin derivatives of the invention may be formulated in any form including liquid formulations, sprays, gels, pastes, emulsions, creams, conditioners, shampoos, and the like. A variety of forms are available though, considering their high commercial demand, hair tonics, creams, conditioners, and shampoos are provided herein. As revealed in the above the Test Example, the cyclosporin derivatives exhibit an excellent hair growth promoting effect, compared to the control.

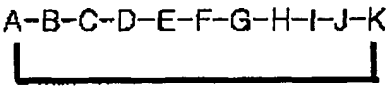
Industrial Applicability

As apparent from the above description, the present invention provides a hair growth promoting agent comprising a cyclosporin A derivative substituted in the 3-position of cyclosporin A as an active ingredient, which exhibits an excellent hair growth promoting effect.

Claims

1. A hair growth promoting agent comprising a 3-position analog of cyclosporin represented by Formula 1, as an active ingredient:

[Formula 1]



in which

A represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine, (2S,3R,4R,6E)-3-sulfhydryl-4-methyl-2-(methylamino)-6-octenoic acid or (2S,4R,6E)-3-oxo-4-methyl-2-(methylamino)-6-octenoic acid;

B represents L-aminobutyric acid (Abu), L-alanine (Ala), L-threonine (Thr), L-valine (Val) or L-norvaline (Nva);

C represents a D-amino acid represented by the general formula 1,

[General formula 1]

CH_3NH-CH(R)-COOH

in which,

R is one selected from the group consisting of hydrogen, C_1-C_6 straight or branched alkyl, alkenyl or alkynyl moieties, substituted or unsubstituted with one or more selected from the group consisting of amino, hydroxy, halo, haloalkyl, ester, alkoxy, cyano, nitro, alkylamino, and dialkylamino, and -X- R' represented by the general formula 2 below,

[General formula 2]

-X- R'

in which,

X is oxygen or sulfur, and

R' is one selected from the group consisting of hydrogen, and C_1-C_6 straight or branched alkyl, alkenyl or alkynyl moieties, substituted or unsubstituted with one or more selected from the group consisting of amino, hydroxy, halo, haloalkyl, ester, alkoxy, cyano, nitro, alkylamino, and dialkylamino;

D represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-valine;

E represents L-valine or L-norvaline;

F represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-leucine;

G represents L-alanine or L-alanine thioamide ([$^7\psi^8$ CS-NH], NH-$CHCH_3$-CS-);

H represents a D-amino acid represented by the general formula 3,

[General formula 3]

-NH-CH(CH_2R)-COOH

in which,

R is hydrogen or -X- R'represented by the general formula 4,

[General formula 4]

-X- R'

in which,

X is oxygen or sulfur, and

R' is one selected from the group consisting of hydrogen, and C_1-C_6 straight or branched alkyl, alkenyl or alkynyl moieties, substituted or unsubstituted with one or more selected from the group consisting of amino, hydroxy, halo, haloalkyl, ester, alkoxy, cyano, nitro, alkylamino, and dialkylamino;

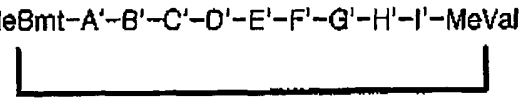
I represents N-methyl-L-leucine, γ-hydroxy-N-methyl-L-leucine or L-leucine;

J represents N-methyl-L-leucine, γ-hydroxy-N-methyl-L-leucine or L-leucine; and,

K represents N-methyl-L-valine or L-valine.

2. The hair growth promoting agent as set forth in claim 1, wherein the 3-position analog of cyclosporin is represented by Formula 2:

[Formula 2]



in which

MeBmt represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine;

A' represents L-aminobutyric acid, L-alanine, L-threonine, L-valine or L-norvaline;

B' represents N-methyl-D-aminobutyric acid, N-methyl-D-norvaline, D-2-(methylamino)hexa-4-ynoyl, D-2-(methylamino)pent-4-ynoyl, D-2-methylthio-sarcosine, N-methyl-O-propenyl-D-serine or N-methyl-D-serine;

C' represents N-methyl-L-leucine, γ-hydroxy-N-methyl-L-leucine or L-valine;

D' represents L-valine or L-norvaline;

E' represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-leucine;

F' represents L-alanine or L-alanine thioamide ([$^7\psi^8$ CS-NH], NH-CHCH$_3$-CS-);

G' represents D-alanine or D-serine;

H' represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-leucine;

I' represents N-methyl-L-leucine, γ-hydroxy N-methyl-L-leucine or L-leucine; and,

MeVal represents N-methyl-L-valine.

3. The hair growth promoting agent as set forth in claim 1, wherein the 3-position analog of cyclosporin is represented by Formula 3:

[Formula 3]

MeBmt-A"-B"-MeLeu-Val-MeLeu-Ala-DAla-MeLeu-MeLeu-MeVal

in which

MeBmt represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine;

A" represents L-alanine, L-threonine, L-valine or L-norvaline;

B" represents N-methyl-D-aminobutyric acid, N-methyl-D-norvaline, D-2-(methylamino)hexa-4-ynoyl, D-2-(methylamino)pent-4-ynoyl, D-2-methylthio-sarcosine, N-methyl-O-propenyl-D-serine or N-methyl-D-serine;

MeLeu represents N-methyl-L-leucine;

Val represents L-valine;

Ala represents L-alanine;

DAla represents D-alanine; and,

MeVal represents N-methyl-L-valine.

4. The hair growth promoting agent as set forth in claim 1, comprising [N-methyl-D-Abu^3] cyclosporin A as an active ingredient.

5. The hair growth promoting agent as set forth in claim 1, comprising [N-methyl-D-Nva^3] cyclosporin A as an active ingredient.

6. The hair growth promoting agent as set forth in claim 1, comprising [D-2-(methylamino)hexa-4-ynoyl^3] cyclosporin A as an active ingredient.

7. The hair growth promoting agent as set forth in claim 1, comprising [D-2-

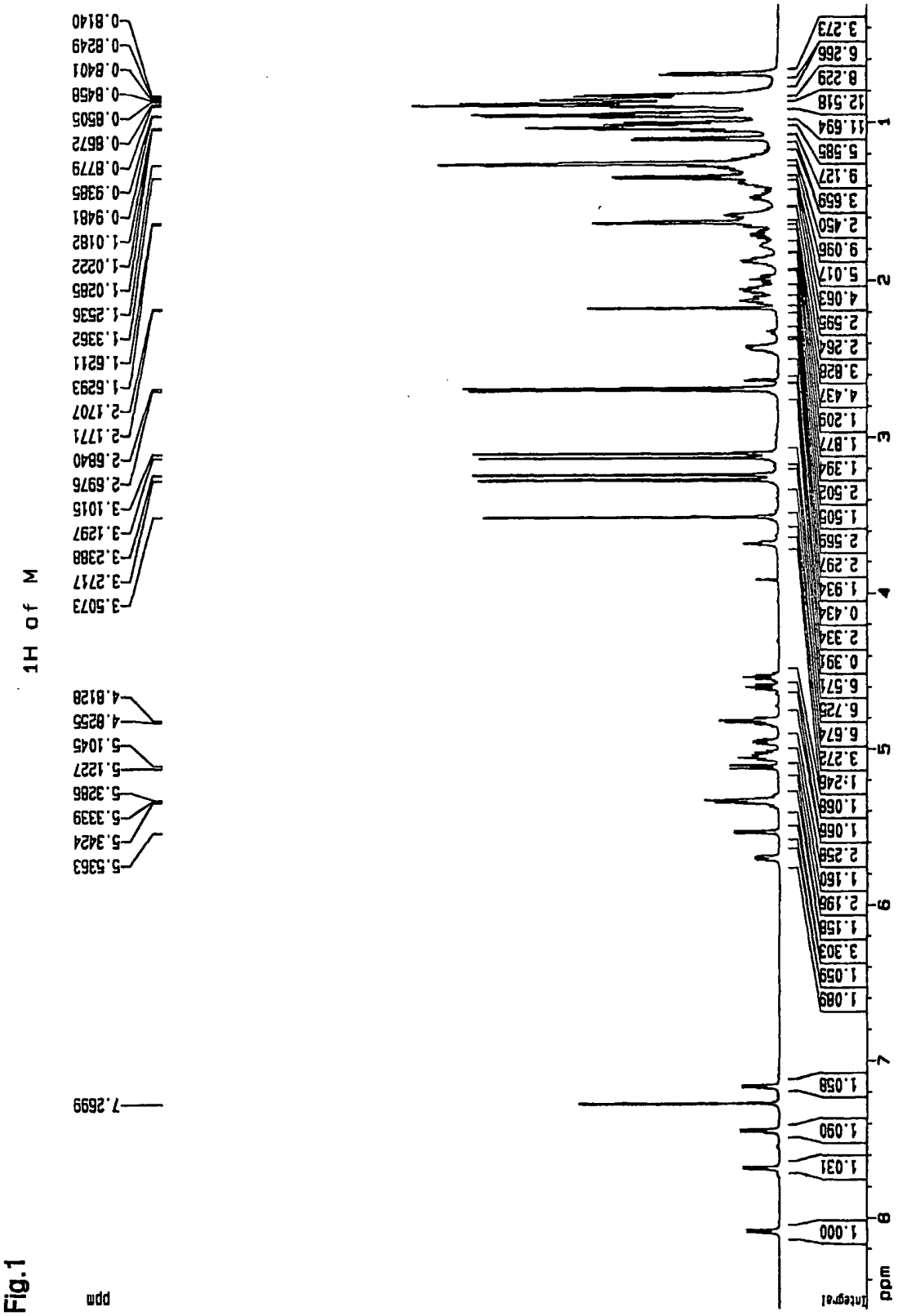
(methylamino)pent-4-ynoyl^3] cyclosporin A as an active ingredient.

8. The hair growth promoting agent as set forth in claim 1, comprising [D-2-methylthio-Sar^3] cyclosporin A as an active ingredient.

9. The hair growth promoting agent as set forth in claim 1, comprising [N-methyl-O-propenyl-D-Ser^3] cyclosporin A as an active ingredient.

10. The hair growth promoting agent as set forth in claim 1, comprising [N-methyl-D-Ser^3] cyclosporin A as an active ingredient.

11. The hair growth promoting agent as set forth in any one of claims 1 to 10, which is formulated in a form selected from the group consisting of liquid formulation, spray, gel, paste, emulsion, cream, conditioner and shampoo.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1.0222
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1.2536
1.3362
1.6211
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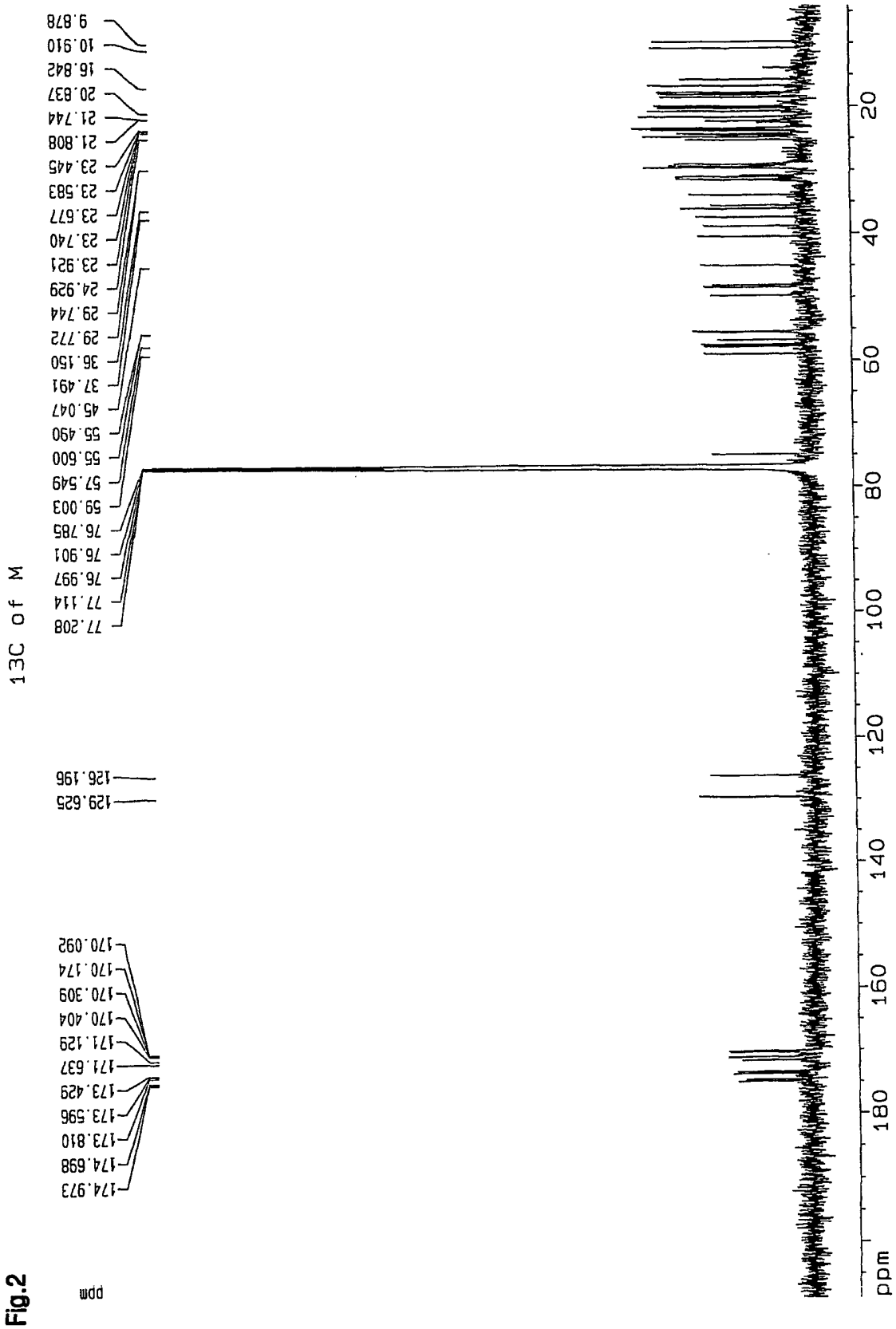
Fig.1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171.129
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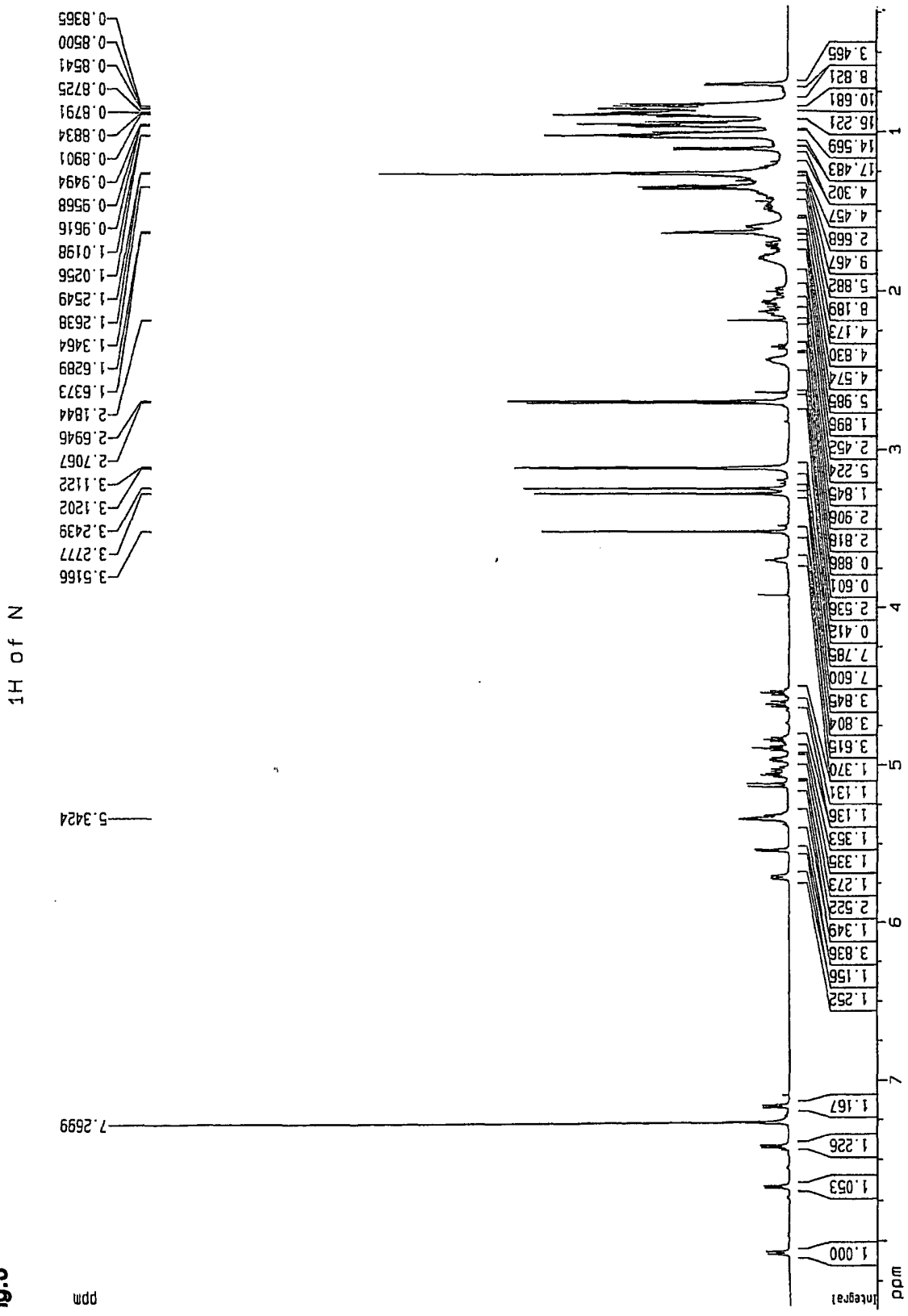
ppm

Fig.2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1.273
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1.131
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7.600
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0.601
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2.818
2.908
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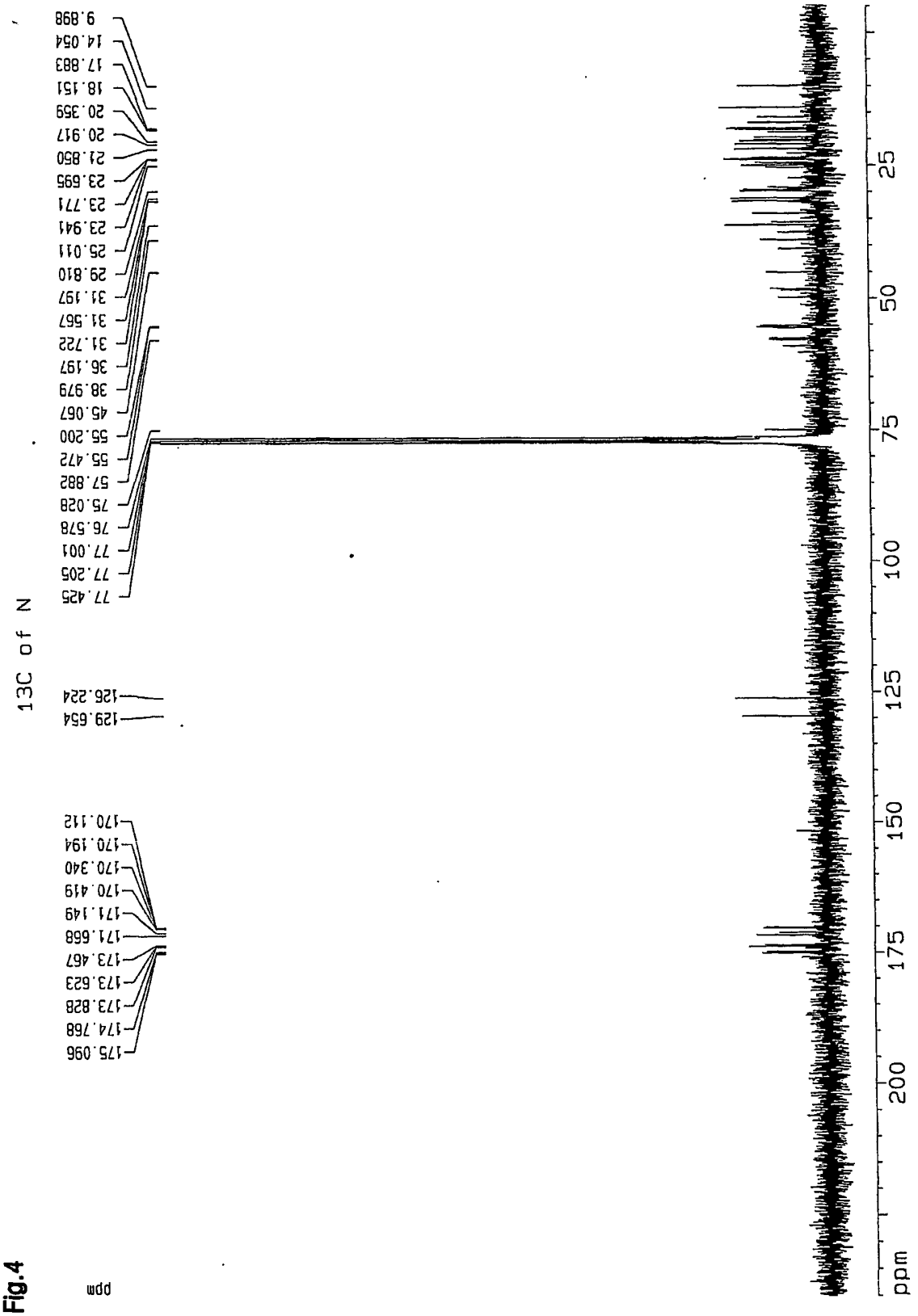
Fig.3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200
ppm

Fig.4

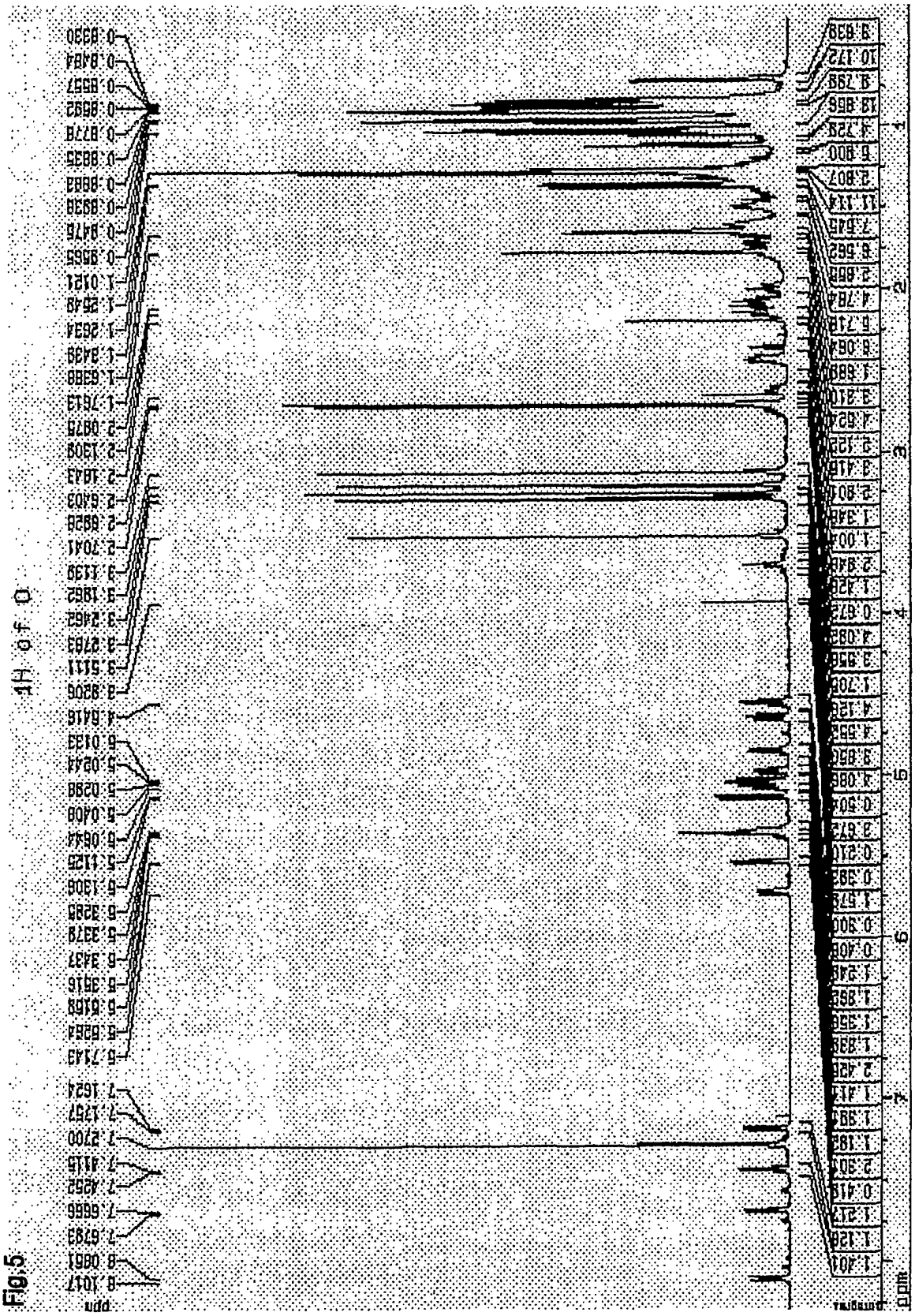
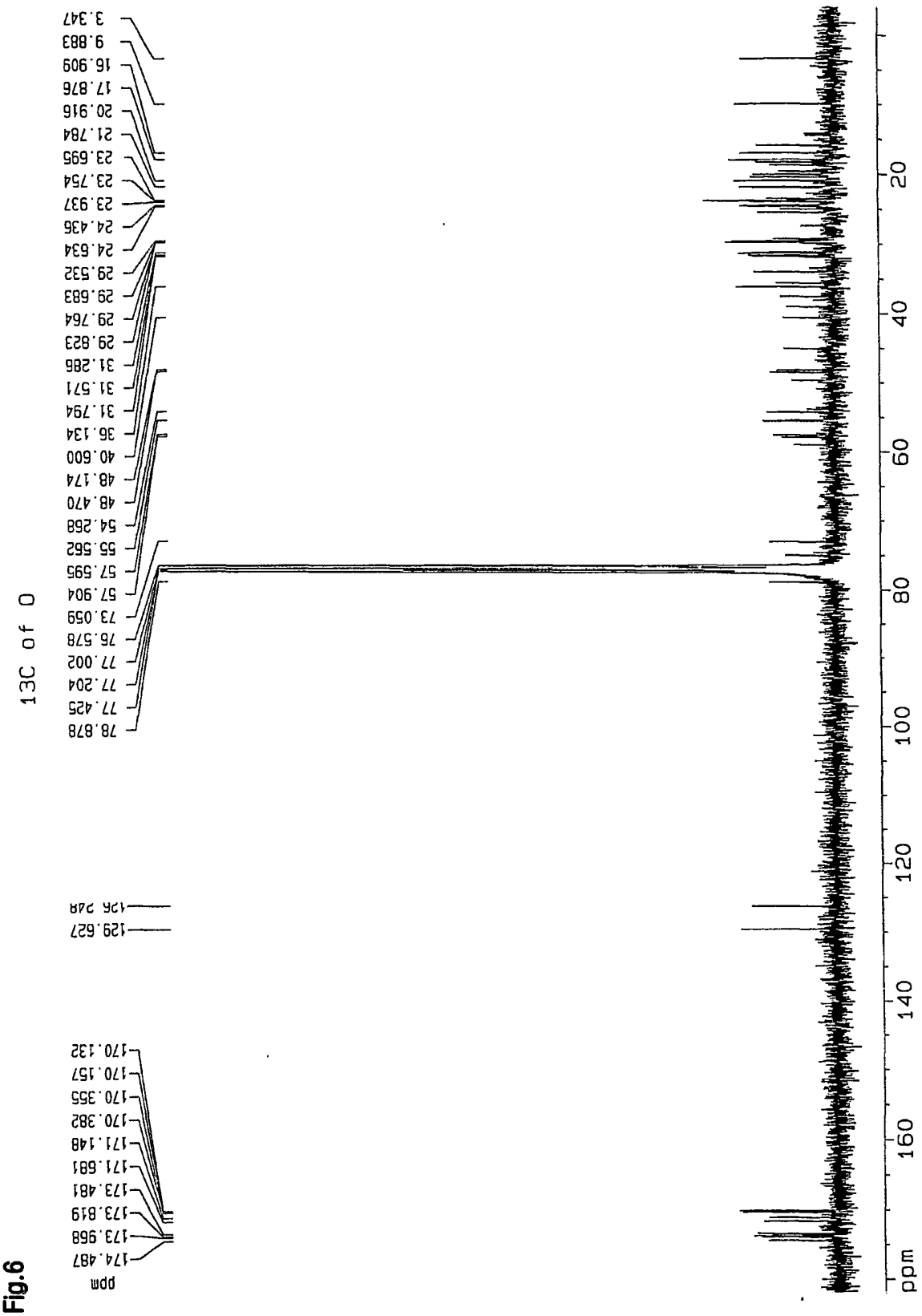


Fig.5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20.916
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23.937
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29.532
29.683
29.764
29.823
31.286
31.571
31.794
36.134
40.600
48.174
48.470
54.268
55.562
57.595
57.904
73.059
76.578
77.002
77.204
77.425
78.878
129.627
174.487
173.968
173.819
173.481
171.681
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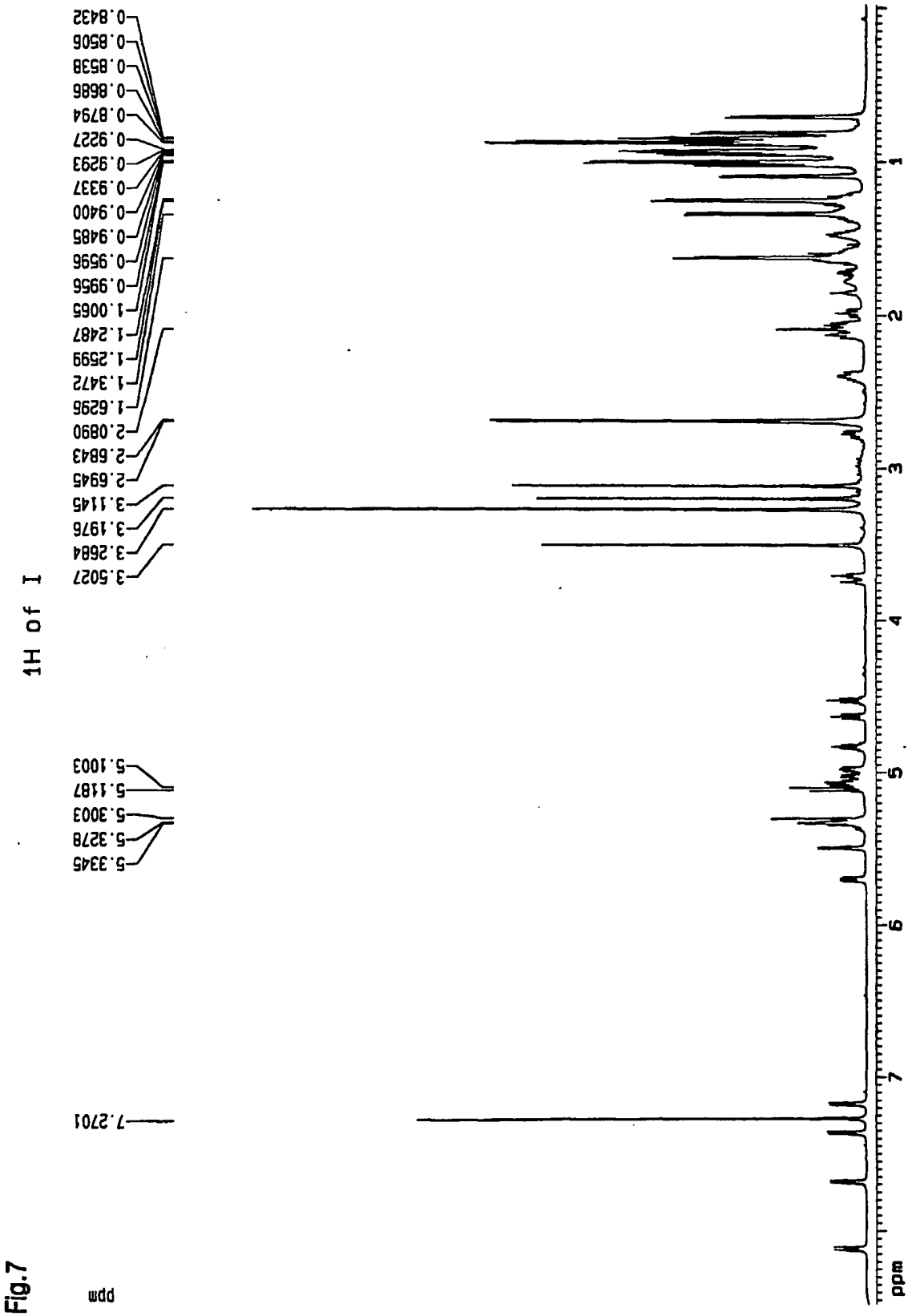
ppm

Fig.6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1.2487
1.2599
1.3472
1.6296
2.0890
2.6843
2.6945
3.1145
3.1976
3.2684
3.5027
5.1003
5.1187
5.3003
5.3278
5.3345
7.2701
1H of I
ppm
1
2
3
4
5
6
7
ppm

Fig.7

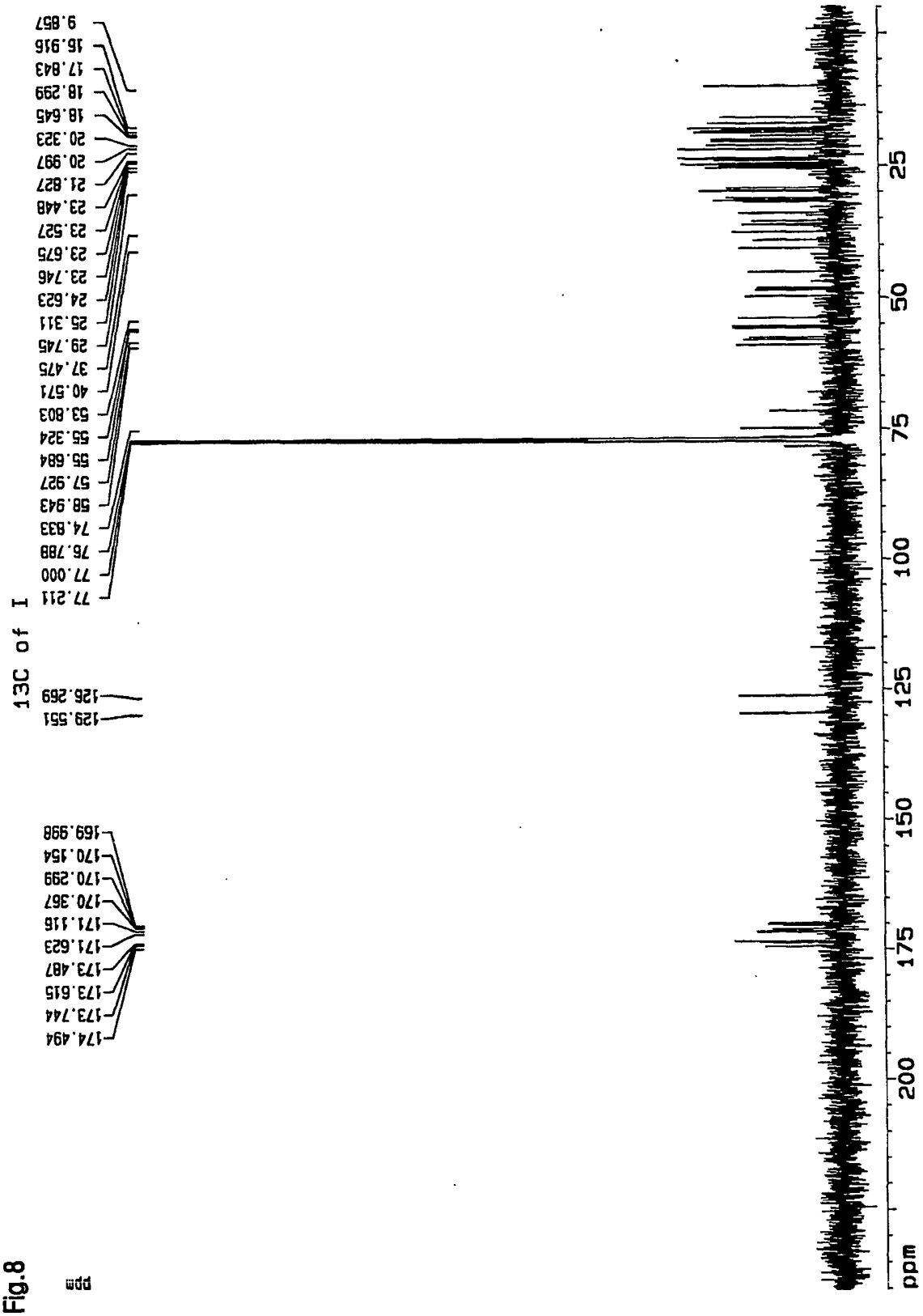

9.857
16.916
17.843
18.299
18.645
20.323
20.997
21.827
23.448
23.527
23.675
23.746
24.623
25.311
29.745
37.475
40.571
53.803
55.324
55.684
57.927
58.943
74.833
76.788
77.000
77.211
125.269
129.551
169.998
170.154
170.299
170.367
171.116
171.623
173.487
173.615
173.744
174.494
13C of I
25
50
75
100
125
150
175
200
ppm

Fig.8

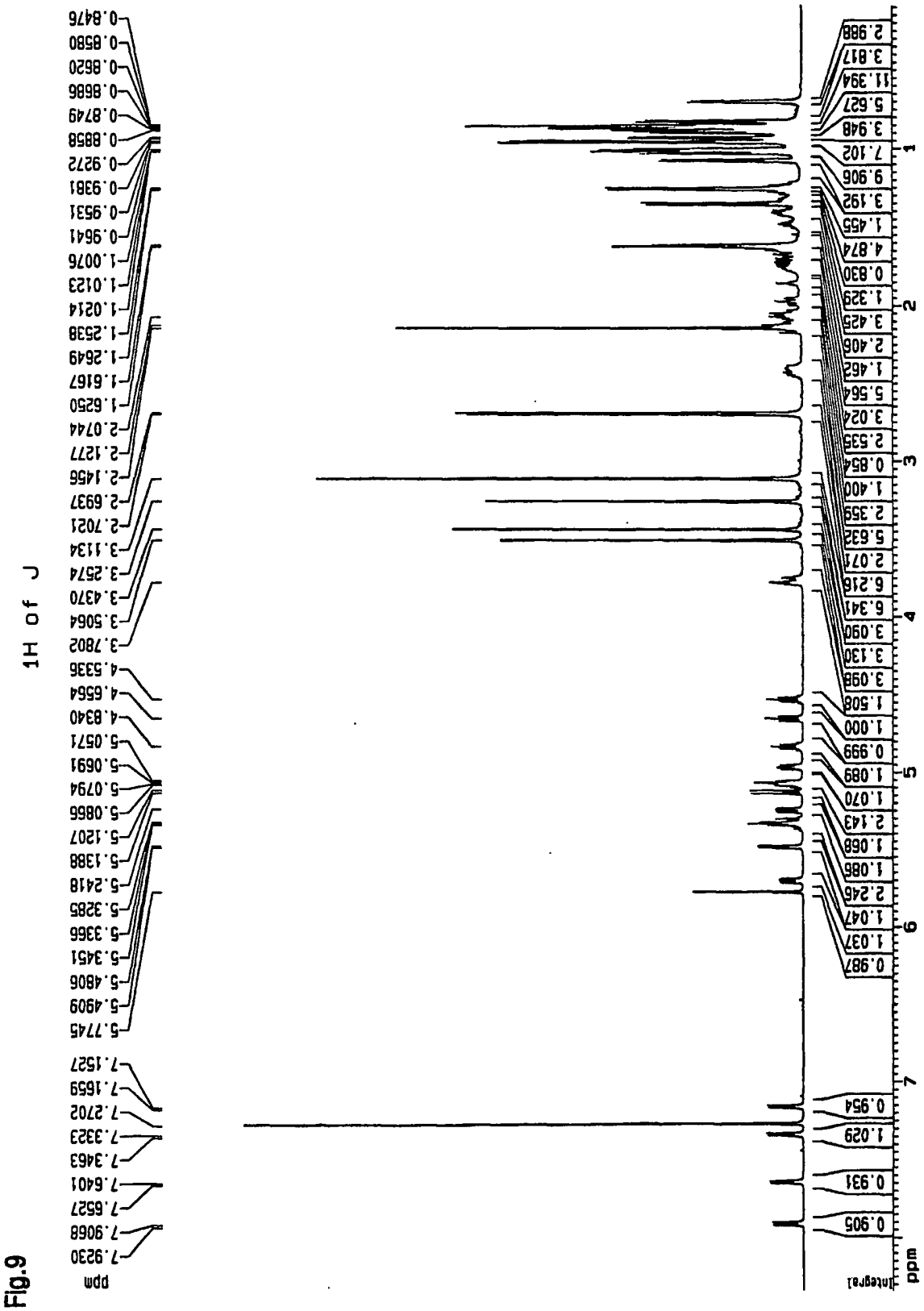


Fig.9

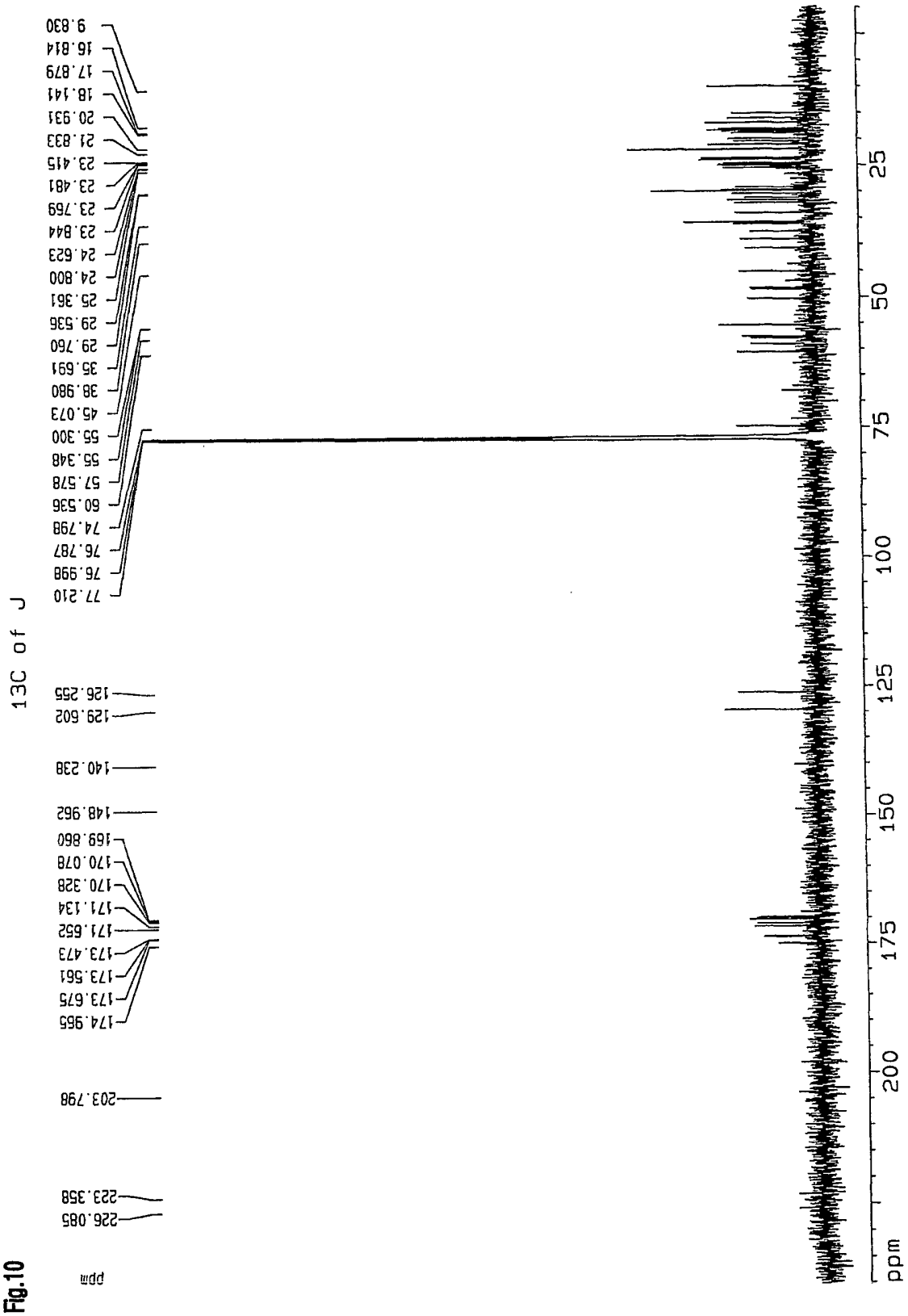

13C of J
9.830
16.814
17.879
18.141
20.931
21.833
23.415
23.481
23.769
23.844
24.623
24.800
25.361
29.536
29.760
35.691
38.980
45.073
55.300
55.348
57.578
60.536
74.798
76.787
76.998
77.210
126.255
129.502
140.238
148.962
169.860
170.078
170.328
171.134
173.652
173.473
173.561
173.675
174.965
203.798
223.358
226.085
ppm
25
50
75
100
125
150
175
200
ppm

Fig.10

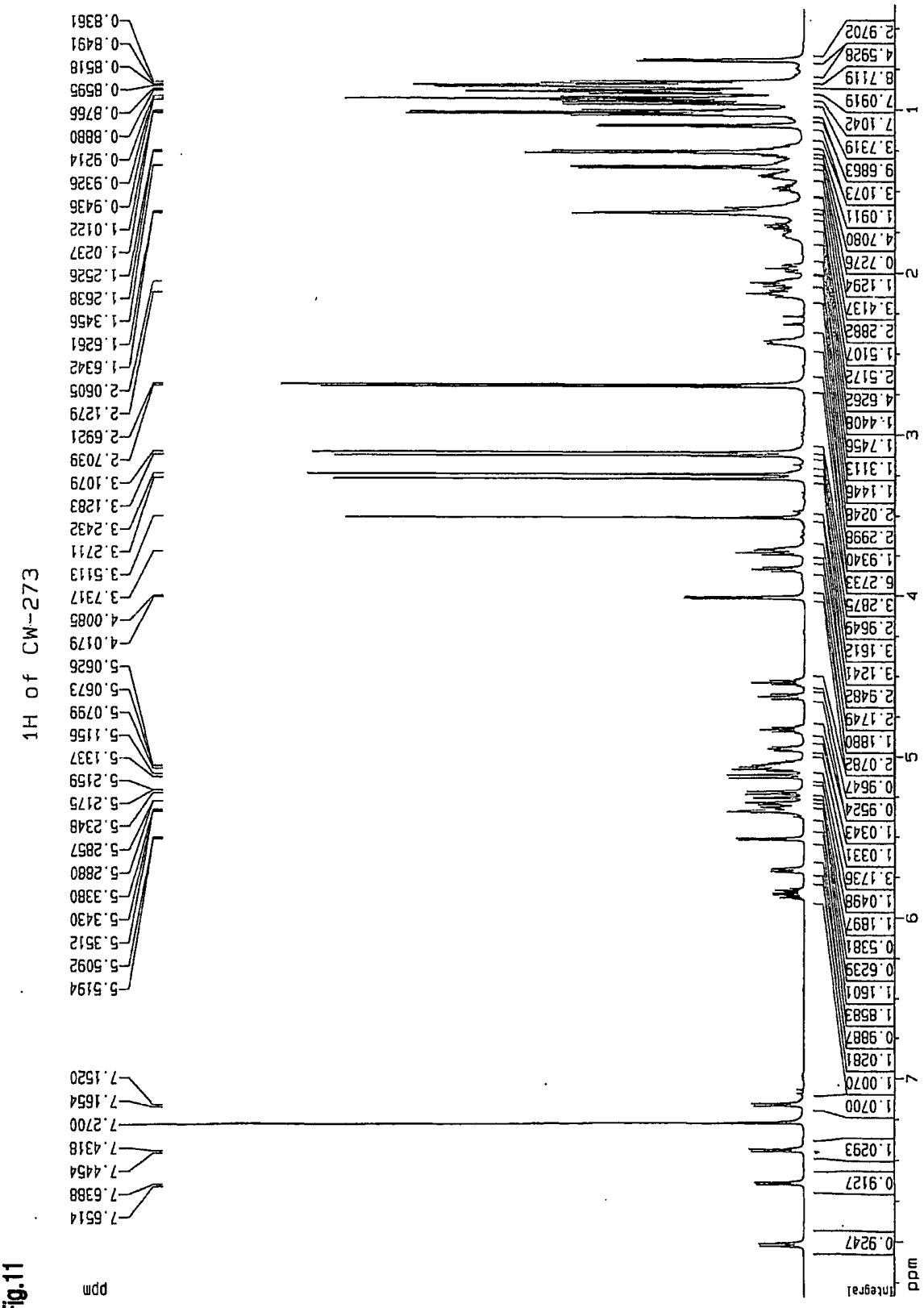
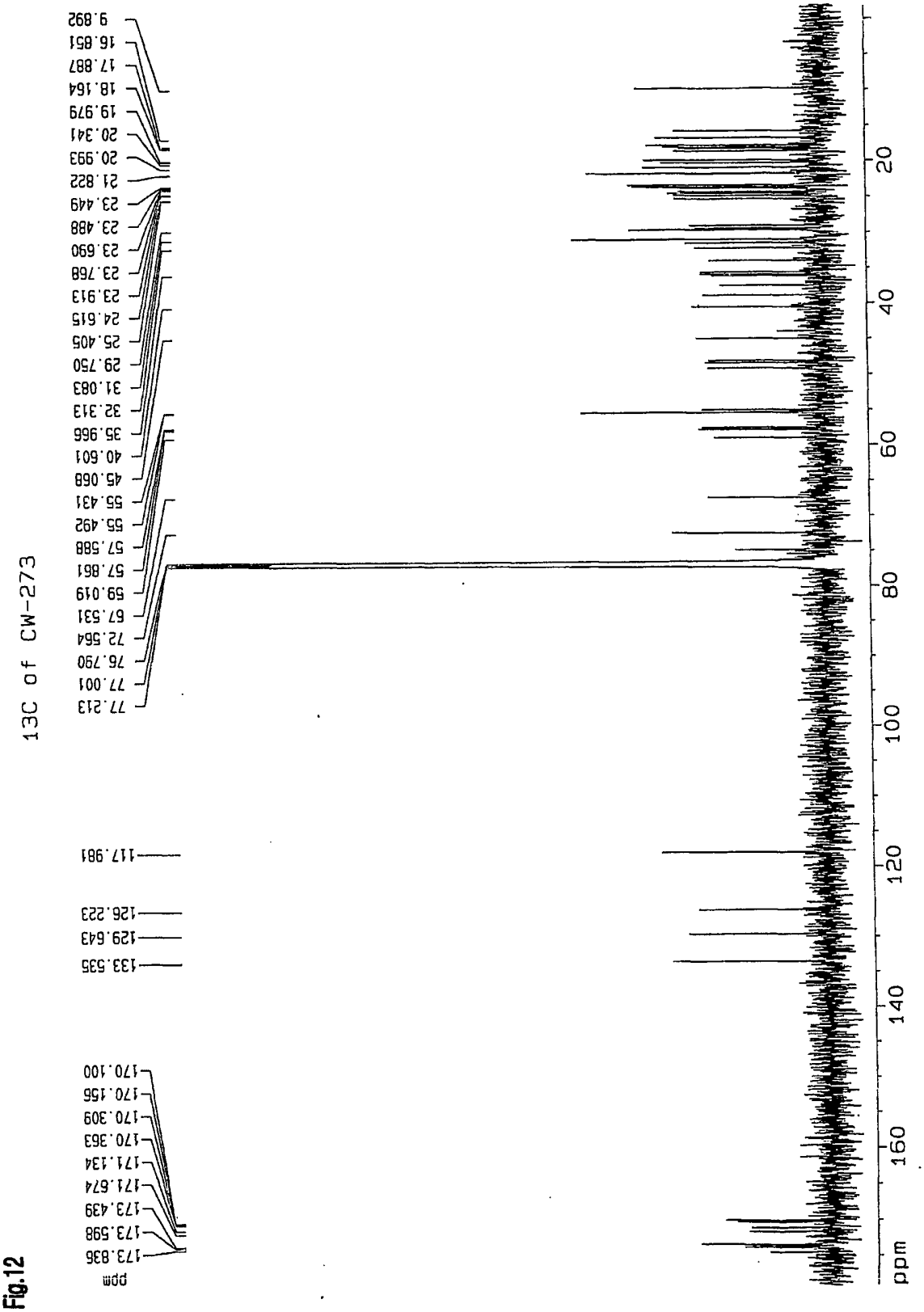


Fig.11


13C of CW-273
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16.851
17.887
18.164
19.979
20.341
20.993
21.822
23.449
23.488
23.690
23.768
23.913
24.615
25.405
29.750
31.083
32.313
35.966
40.601
45.068
55.431
55.492
57.588
57.861
59.019
67.531
72.564
76.790
77.001
77.213
117.981
126.223
129.643
133.535
170.100
170.156
170.309
170.363
171.134
171.674
173.439
173.598
173.836
ppm
20
40
60
80
100
120
140
160
ppm

Fig.12

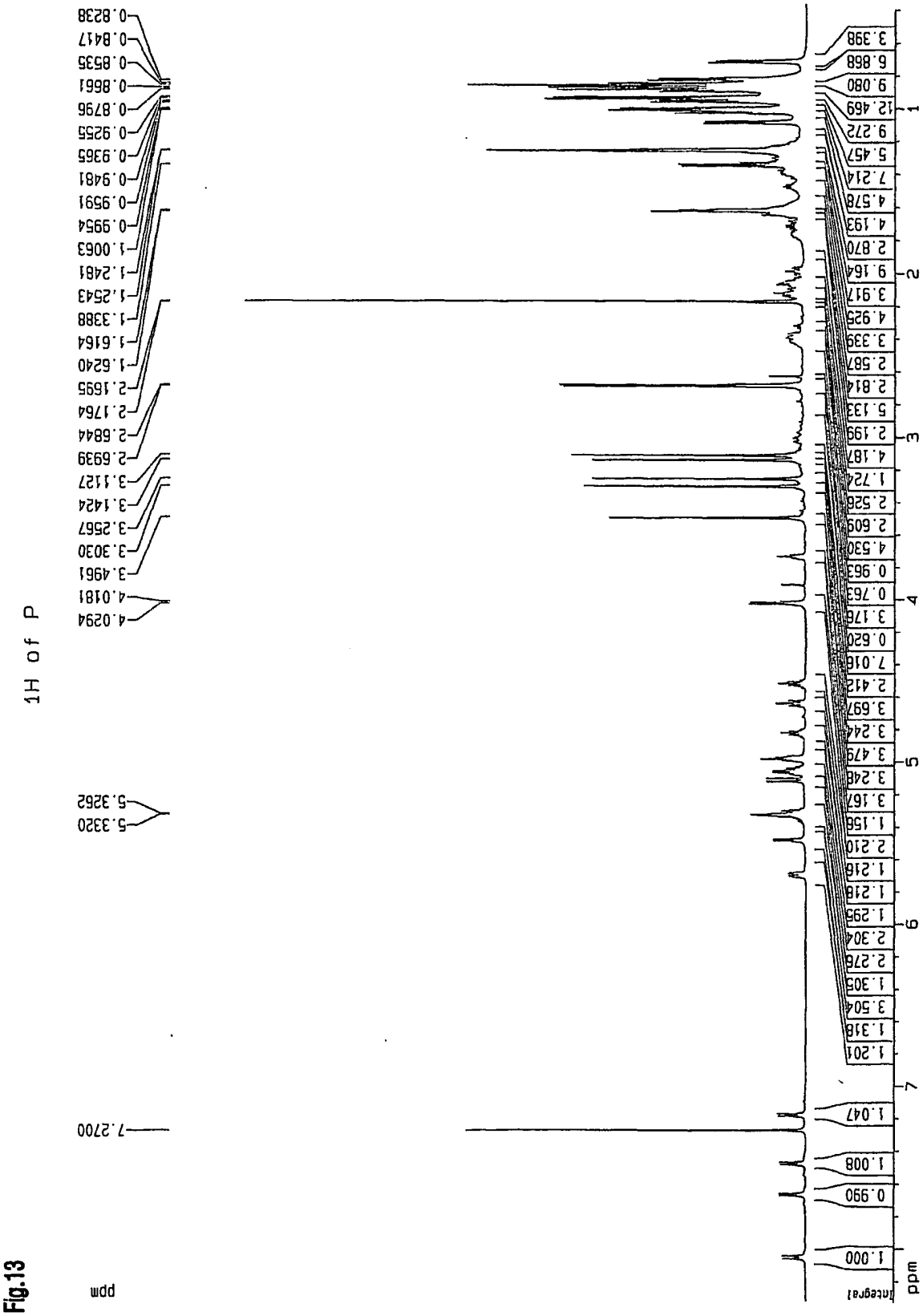
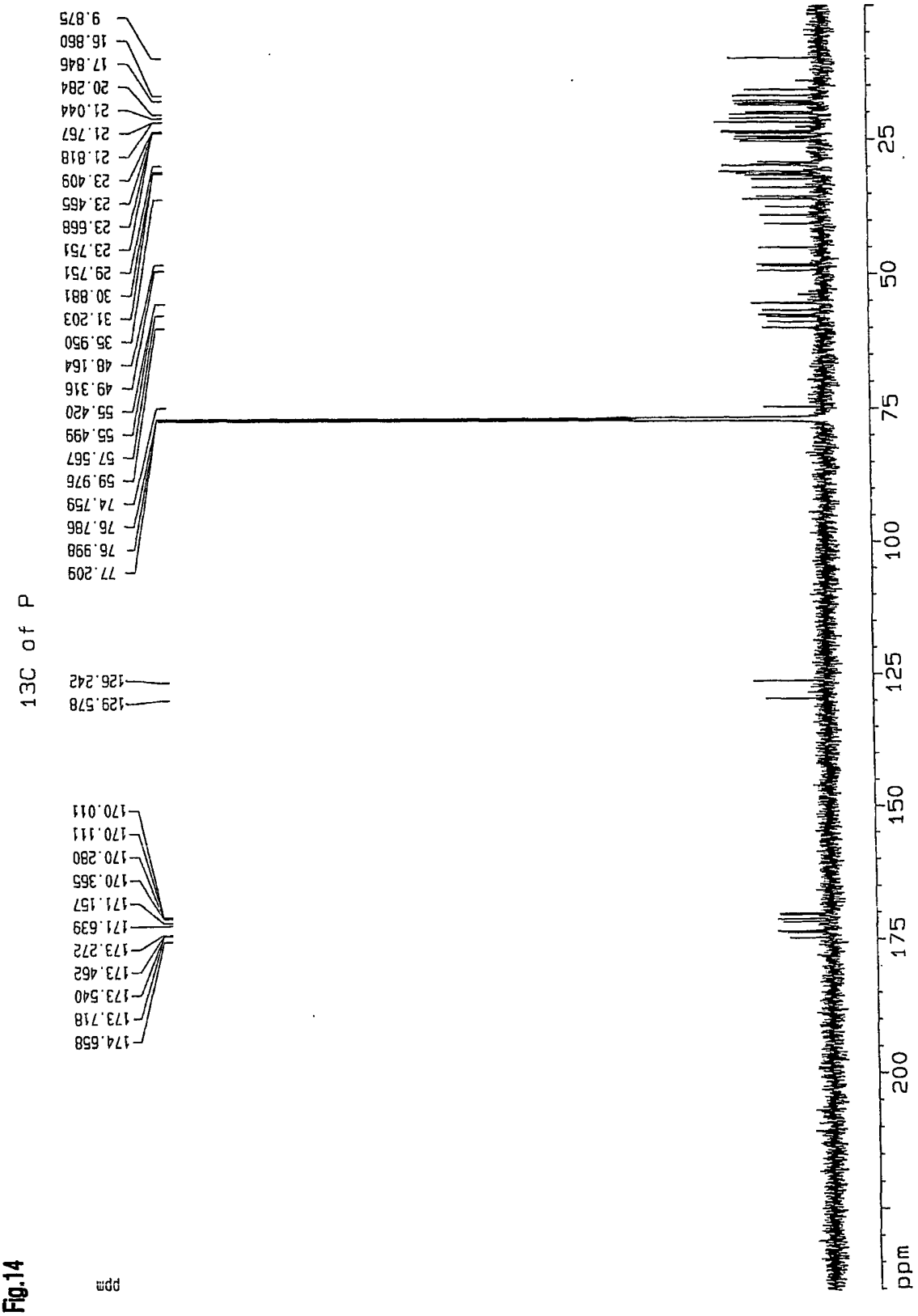

1H of P
ppm
Integral
0.8238
0.8417
0.8535
0.8661
0.8796
0.9255
0.9365
0.9481
0.9591
0.9954
1.0063
1.2481
1.2543
1.3388
1.5164
1.6240
2.1695
2.1764
2.6844
2.6939
3.1127
3.1424
3.2567
3.3030
3.4961
4.0181
4.0294
5.3262
5.3320
7.2700
3.398
6.868
9.080
12.469
9.272
5.457
7.214
4.578
4.193
2.870
9.164
3.917
4.925
3.339
2.587
2.814
5.133
2.199
4.187
1.724
2.526
2.609
4.530
0.963
0.763
3.176
0.620
7.016
2.412
3.697
3.244
3.479
3.248
3.167
1.156
2.210
1.216
1.218
1.295
2.304
2.276
1.305
3.504
1.318
1.201
1.047
1.008
0.990
1.000

Fig.13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16.860
17.846
20.284
21.044
21.767
21.818
23.409
23.455
23.668
23.751
29.751
30.881
31.203
35.950
48.164
49.316
55.420
55.499
57.567
59.976
74.759
76.786
76.998
77.209
126.242
129.578
170.011
170.111
170.280
170.365
171.157
171.639
173.272
173.462
173.540
173.718
174.658
13C of P
25
50
75
100
125
150
175
200
ppm

Fig.14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR02/00879

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KR, JP ; IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), MEDILINE(STN), USPATFULL, NPS, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5807820 A (Novatis AG) 15 SEPTEMBER 1998 See column 1. line 53 - column 1. line 57. Claim 1	1 - 11
A	US 5284826 A (Sandoz Ltd.) 8 FEBRUARY 1994 See claims 1 - 6	1 - 11
A	James P. Jacobs et al., "Use of topical minoxidil therapy for androgenetic alopecia in women", International Journal of Dematology, 1993, Vol. 32, No. 10, pages 758 - 762 See the whole document	1 - 11
A	Maurer M. et al., "Hair growth modulation by topical immunophilin ligands : Induction of anagen, inhibition of massive catagen development and relative protection from chemotherapy-induced alopecia", 1997, Vol. 150, No. 4, pages 1433 - 1442 See the whole document	1 - 11
A	Yamamoto S. et al., "Hair growth stimulating effects of cyclosporin A and FK506, potent immunosuppressants", 1994, Vol. 7 suppl., pages S47 - S52 See the whole document	1 - 11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
19 SEPTEMBER 2002 (19.09.2002)	19 SEPTEMBER 2002 (19.09.2002)

Name and mailing address of the ISA/KR
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Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
KANG, Choon Won
Telephone No. 82-42-481-5608

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR02/00879

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
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		ES	T3	2092500	01-12-96
		FI	A0	903706	23-07-90
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		PT	A	94790	20-03-91
		PT	B	94790	30-04-97
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		ZA	A	9005823	25-03-92